CLINICOPATHOLOGICAL CORRELATION OF BREAST NEOPLASMS WITH HORMONE RECEPTOR STUDY IN SELECTED CASES

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CHENNAI - TAMILNADU

Department of Pathology,
Madurai Medical College and
Government Rajaji Hospital,
Madurai.

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CERTIFICATE

This is to certify that the dissertation entitled **"CLINICOPATHOLOGICAL CORRELATION OF BREAST NEOPLASMS WITH HORMONE RECEPTOR STUDY IN SELECTED CASES"** is submitted by Dr. B.Shobana to the faculty of Pathology, The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfilment of the requirement for the award of M.D. Degree in Pathology is a bonafide work carried out by her during the period June 2010 – July 2012 under my direct supervision and guidance.

Professor and Head,
Department of Pathology,
Madurai Medical College,
Madurai.

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CONTENTS

INTRODUCTION

Breast cancer is a multifactorial disease which is having distinct biological subtypes. They have a broad spectrum of clinical, pathological and molecular characteristics resulting in different prognostic and therapeutic applications. Therefore, every lump in the breast should be considered as a malignant lesion until proved otherwise.

As breast is one of the frequent sites which is under the influence of hormones, major hormonal changes during adolescent period, child bearing period and at the time of menopause will affect the mammary tissue. Breast cancer is one among the frequently encountered malignancies in the world among females. There should be enough knowledge about its epidemiology at the regional as well as in worldwide basis and this will provide a way for its effective control.

Many of the Indian literature report that the age incidence of breast cancer in the Indian females is somewhat prior to the western population. Among urban females, carcinoma breast has come up as the leading cause of cancer-related mortality[6] and has overtaken carcinoma cervix. With the knowledge of complexity and heterogeneity of breast cancers, intensive efforts have been undertaken to study the correlation between clinical characteristics and the histopathological as

well as molecular features. Also, there is a steady and persistent work up in identifying certain predictive factors to deal with the disease prognosis and treatment strategy.

In low and middle income countries, Breast cancer related mortality has been in the range of 55% of all new cases per year (Curado et al, 2007). In India the incidence of breast cancer constitutes about one third to one fourth that in USA but still stands as the leading cause of cancer among women (Ferlay et al, 2004, Datta et al 2012).

Though the incidence is lower, the total number of cases and the mortality is high because of the population burden, insufficient screening facilities and lack of education. To reduce this increasing load of mortality, we need to consider the importance of early detection and the availability of systemic therapy and for this, we should have a better understanding of the trend, age group involved and other risk factors.

Even if, a great advancement has emerged in the management of breast cancer, the concept in the management of breast cancer is to bring forward an individual based treatment plan to avoid excessive and ineffective treatment that can cause unnecessary morbidity and mortality. Estrogen receptor (ER) which has been

discovered in 1962[47] has become the first molecule with great effectiveness in the intervention of invasive Breast cancer.

Nowadays, breast carcinoma is considered as a distinct and exclusive disease in oncology and the specific biologic markers - ER, PR are utilised to predict the hormonal response and serve as a guide for the therapeutic plan. Hormonal receptor positive and negative cases have different biological behaviour, distinct treatment protocol and prognostic implication.

This study aims at correlating the factors like age of the patient, clinical presentation, histological grade, stage and the hormonal receptor status with respect to menopausal status and different histological types of breast carcinomas. An attempt has been made to evaluate the various morphological patterns of the malignant lesions of the breast and their age distribution from the mastectomy specimens along with the axillary lymph node dissection in the Department of pathology, Madurai medical college, Madurai.

With the help of the hormonal receptor (ER, PR) assessment, the prognostic assessment and the treatment modality of breast cancer can be done with precision.

AIM OF THE STUDY

- To study the frequency of occurrence of malignant lesions in the mastectomy specimens received from Government Rajaji hospital, Madurai to the Department of pathology, Madurai Medical College, Madurai.
- To find out the incidence of malignant lesions with regard to age, sex, laterality of the breast and menopause.
- To study the histological types of breast carcinomas.
- To determine the various prognostic parameters of breast carcinomas.
- To determine the significance of histological grade among the breast carcinomas.
- To demonstrate the hormone receptor status such as Estrogen and Progesterone receptor (ER, PR) in different age groups.
- To analyse the hormone receptor status in relation to premenopausal and postmenopausal age group.
- To find out the hormone receptor status in different histological types of breast carcinoma.

REVIEW OF LITERATURE

Although antiquity incorporates an overview of many decades, a few recent years are included to summarise achievements and failures. A historical evaluation conveys a hope for future improvements about the diagnosis and management of breast cancer.

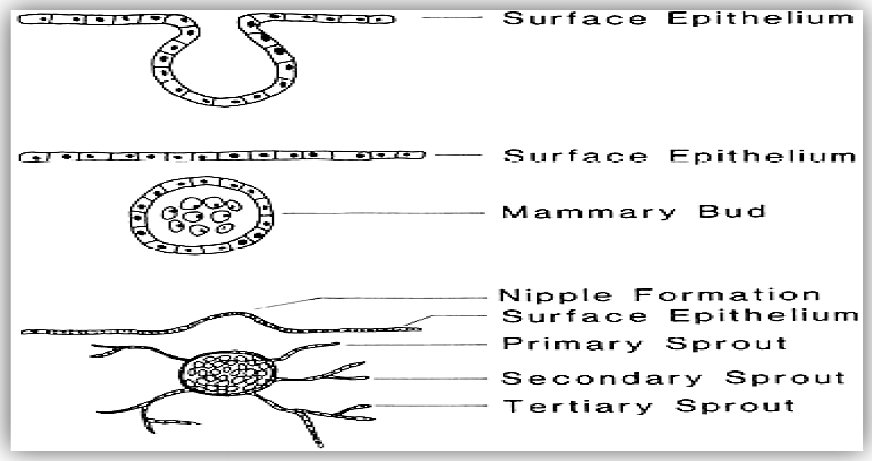
Diseases of the breast have drawn attention of medical interest as long as 3000 B.C. The Edwin smith of Egyptian pyramics age (3000 – 2500 B.C.) described many cases of breast cancer. In reality, breast carcinomas were the first human cancers discovered. The Egyptian surgeons emphasized that it was difficult to remedy hard lumps of the breast.[47]

In 1656, Marcus Aurelins Saverinus was the first surgeon who removed the enlarged axillary lymph glands at the time of breast amputation. He advocated the excision of the benign tumours in the breast because of the increased relative risk of them becoming malignant. Leonides was the first to emphasize that nipple retraction is a significant clinical sign of breast malignancy[47]. In 1560, the relation of breast cancer to the axilla and its extension was documented by Ambroise Paire, a French army surgeon.

DEVELOPMENT OF MAMMARY GLAND:[22]

The breast is a complex apocrine gland that develops in to a functional organ in woman but becomes a rudimentary organ in males.

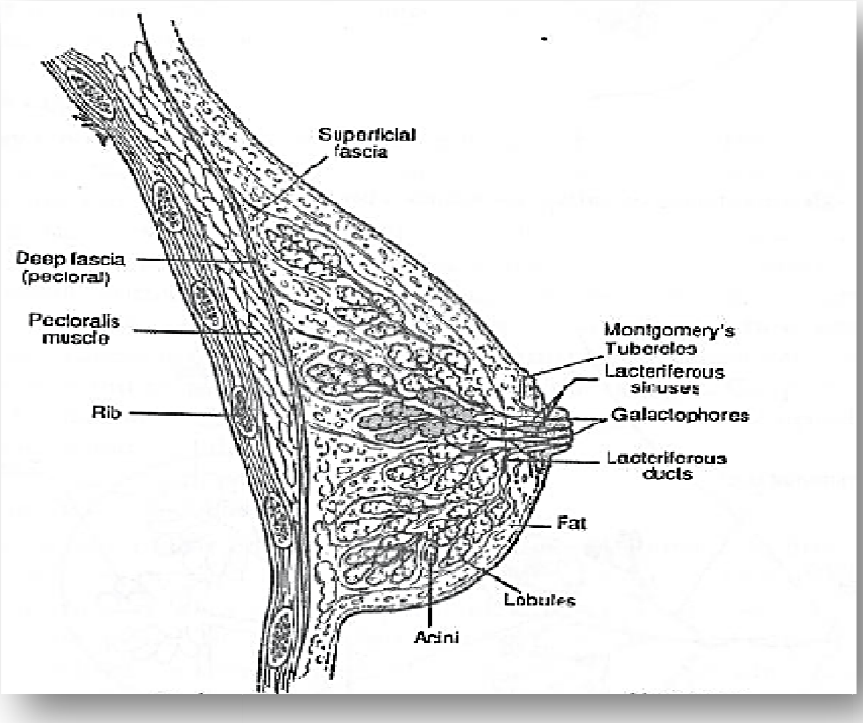
In the human embryo, the ectoderm becomes thickened along a line which extends from the axilla to the inguinal region and this thickening forms the mammary ridges. From a part of this mammary line, each mammary gland develops that overlies the pectoral area at sixth week of development of foetus.[34]



Presumptive cords are developed from the epidermis in the second trimester and grow into the underlying dermis. They subsequently become canalised to form the ductal structures. The terminal parts of cords proliferate to form the secretory elements. During puberty and pregnancy, ducts and secretory elements undergo extensive development. Accessory breast which is observed in 1% of the females may be found in neck, cheeks, femoral triangle and vulva.

ANATOMY[3]:

The structure of the breast consists of skin, parenchyma and stroma. The skin covers the gland and presents a conical projection called nipple at the level of fourth intercostal space. It contains circular and longitudinal smooth muscle fibres. The skin surrounding the base of the nipple is pigmented and forms areola which is rich in modified sweat glands. The parenchyma is composed of glandular tissue which secretes milk. The gland consists of 15-20 lobes. Each lobe is a cluster of alveoli, drained by lactiferous duct which has a dilatation at its termination called lactiferous sinus and open in to the nipple. The stroma is partly fibrous and partly fatty which anchors the skin and gland to pectoral fascia.



Vessels and Nerves:-

The arteries arise from the axillary, the intercostals, and the internal mammary arteries. The veins form an anastomotic circle and end up in the axillary and internal mammary veins. The nerves arise from the lateral and anterior cutaneous branches of the fourth, fifth, and sixth thoracic nerves. Lymph from the breast drains in to axillary nodes, internal mammary nodes, supraclavicular and posterior intercostal nodes.

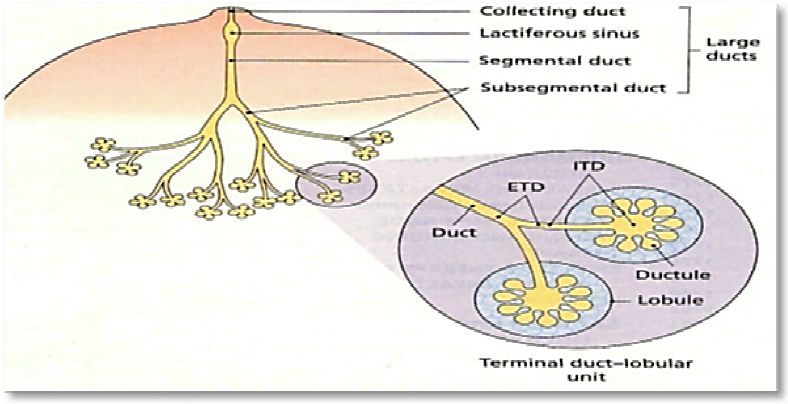
HISTOLOGY[4]:

Lobule is the functional unit of the breast. A lobule consist of numerous acini (glands) lined by two-layered epithelium.

- Outer flattened myoepithelial cell,

- Inner cuboidal or columnar cell.

The acini drain its secretions into a terminal duct. Each terminal duct and its acini are together called as the Terminal Duct Lobular Unit (TDLU) which is thought to be the origin of breast tumours.The terminal duct ends in a sub-segmental duct, segmental duct, and terminates into lactiferous duct. There are 15 – 20 lactiferous ducts which terminate into the nipple. Immediately below the nipple, lactiferous sinus is formed by the dilatation of lactiferous duct.



PHYSIOLOGICAL CHANGES[4]:

In accordance with the state of activity, the epithelium of the breast differs. In the gland of nulliparous woman, the alveoli are small and filled with a mass of granular polyhedral cells. During pregnancy the alveoli enlarge and multiply. During lactation, in the centre of the alveoli, the cells undergo fatty degeneration, and are extruded in the first milk, as colostrum corpuscles. The peripheral cells of the alveoli remain as single short columnar cells. The lining epithelium becomes flattened when the acini become distended with secretion.

HORMONES ACTING ON BREAST[42]:

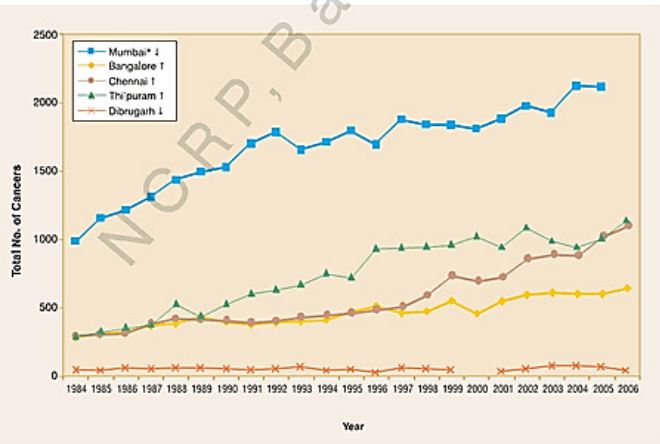
Breast development is stimulated by the hormones estrogen and progesterone. Estrogen causes proliferation of mammary ducts and progesterone causes growth of lobules and alveoli. During pregnancy the large amount of estrogen secreted by the placenta causes the ductal system to grow, with other hormones like growth hormone, prolactin, adrenal glucocorticoids and insulin.

Oxytocin and prolactin are essential for milk secretion and ejection during lactation.

INCIDENCE AND EPIDEMIOLOGY:

Carcinoma affects all the communities worldwide. Out of the 10 million people who are diagnosed with carcinoma, more than 6 million people die of cancer every year[52]. Breast carcinoma stood first among the malignancies in women. On a Worldwide basis, it causes 3,76,000 deaths per year and 9,00,000 new cases are diagnosed every year.[31]

On accounting the prevalence in Indian women, carcinoma cervix and breast account for 60% of cases, of which the incidence of breast carcinoma is 10.4%. A study conducted by WHO[31] (1999) documented that Chennai has the highest incidence among all the centres in India (ie) 26/1,00,000 women. The mean age for the incidence is 42 years[53].



Due to the widespread use of mammography,[50] the detection of breast carcinoma has been increased. However, the mortality from breast carcinoma is somewhat reduced which may be because of improved therapy[50].

RISK FACTORS:

The increased prevalence of the disease has given a way to the vigorous study about risk factors. Strong and prolonged estrogen stimulation with a genetically susceptible background has been documented as a common risk factor[52, 44, 45].

1. Place of birth: Incidence of breast cancer is common in developed countries than in developing countries.

2. Family history: Females who have first degree relatives with breast cancer have a two to three times more risk that of the general population.

3. Nulliparity: Unmarried women and nulliparous women have more risk for developing breast cancer. Also, late age at first pregnancy (30 years and above) has been documented as a risk factor. Multiparous women had 50% risk reduction in comparison with nulliparous females.

4. Menstrual history: Increased risk is associated with early menarche and late menopause due to estrogenic stimulation.[53]

5. Proliferative Breast disease: Increased risk is associated with prior biopsies of the breast showing fibrocystic disease (Fig 7) and atypical ductal hyperplasia (relative risk 4.0 – 5.0).[53]

6. Socio economic group: Increased risk is associated with high socio- economic group. The risk of developing breast cancer within the next 20 years period at the age of 50 is 1 in 26 among Asian countries.

Additional risk factors are also found out, but there is a lack of definitive relationship[53].

1. Estrogen exposure: Postmenopausal hormone replacement therapy and oral contraceptive drugs usage are affiliated with the risk of developing breast cancer. Oophorectomy reduces the risk of breast cancer by 75%.

2. Carcinoma of contralateral breast and endometrium: Approximately 1% of females with breast cancer develop a breast cancer in the contralateral breast per year.[53]

3. Radiation exposure: Those who are exposed to therapeutic radiation and atom bomb survivors are prone for development of breast cancer.

4. Geographic influence: Breast cancer incidence rates are about four times increased in the United States and Europe than in other countries.

5. Diet: High fat diet and obesity have increased risk.

6. Breast feeding: The longer period of breast feeding is associated with reduction in the risk of breast carcinoma.

7. Exercise: Risk is reduced in association with regular exercise.

ETIOLOGY AND PATHOGENESIS[53]:

The major risk factors for the genesis of breast cancers are hormonal and genetic (family history).

Breast cancers can be divided into

1) Sporadic breast carcinoma.

2) Hereditary breast carcinoma.

HEREDITARY BREAST CARCINOMA:

About 25% familial breast cancers can be ascribed to two highly penetrant autosomal dominant genes BRCA 1 and BRCA 2, located in 17q21 and 13q12.3 respectively. They function on similar pathways and interact with multi protein complexes. Both act as tumour suppressor genes and loss of function leads to breast carcinoma due to proliferation of breast epithelium. BRCA 1 interacts with estrogen receptor and is involved in X- Chromosome activation.

BRCA1mutations are more common in medullary carcinoma (67%) and mucinous carcinoma (55%), BRCA2 mutation does not have a definite morphologic appearance.[52,64]

SPORADIC BREAST CARCINOMA:

The vital risk factors for sporadic breast cancer are attributed to hormone exposure, age at menarche and menopause, gender, and estrogens administered exogenously. These carcinomas are associated with postmenopausal women and they over express the estrogen receptor. [53]

Breast carcinoma can occur at any age, but is rare in patients younger than 25 years. The peak incidence is 45-60 years. It is conventional to subdivide carcinoma of the breast into two main pathologic categories – in situ carcinoma and invasive carcinoma.

WHO CLASSIFICATION OF BREAST TUMOURS[64] is included in Annexure II.

HISTOLOGIC TYPES OF BREAST CARCINOMA:

The important determinants in the morphologic analysis of breast carcinoma are

1. Whether the tumour is confined within the epithelium (in situ carcinoma) or has stromal invasion (invasive carcinoma).

2. Whether it belongs to the ductal type or lobular type[26,80,81].

INVASIVE CARCINOMA:

Tumours in which stromal invasion is appreciable are termed invasive whether an in situ component is present or not. Two major categories of invasive cancers are ductal type and lobular type[44].

The classification and distribution of various histological types of invasive carcinomas is as follows:

Classification of histological types with distribution[53]:

Invasive carcinoma	**Percentage(%)**
Invasive carcinoma NOS type	79
Lobular carcinoma	10
Tubular/Cribriform carcinoma	6
Mucinous carcinoma	2
Medullary carcinoma	2
Papillary carcinoma	1
Metaplastic carcinoma	<1

INVASIVE DUCTAL CARCINOMA - NOS TYPE (IDC-NOS):

Rosen (1975) et al says that this type constitutes 65-80% of breast carcinomas. According to WHO, the classification of Invasive ductal carcinoma - NOS type tumour is one of exclusion: "Invasive ductal carcinoma is the most common malignant tumour, not falling into other categories of invasive breast carcinoma"[64]. Grossly, they have an irregular, stellate outline or nodular configuration with greyish white cut surface and yellow streaks (Fig 1). It can be associated with Paget's disease of the nipple presenting as eczematous changes of the nipple (Fig 5).

Microscopically, WHO classification requires a non-specialized pattern in more than 50% of the tumour area to be termed as NOS- type. Typically, infiltrative margins and trabecular, diffuse sheet like, acinar, nested, comedo patterns (Fig 2) are seen in combinations[44,45].

Paget's disease of the nipple shows proliferation of atypical cells in the epidermis with large nuclei and clear cytoplasm (Toker cells) (Fig 6). Hormone receptor studies of IDC-NOS type shows that 70-80% of this tumour type had Estrogen, Progesterone receptor positivity[44,64].

INVASIVE LOBULAR CARCINOMA: (ILC)

Foote and Stewart (1946) et al identified the term Infiltrating Lobular Carcinoma. Tavassoli (1992) documented that ILC of breast showed small cells with linear pattern of growth. This type constitutes 4.9-15% of all invasive breast cancers[64]. It is evidenced that it is commonly multicentric in comparison with other tumour types[44]. It is difficult to define it grossly because they are poorly delimited tumours. Microscopically, the cells are non-cohesive with eccentrically placed round or oval nuclei with small nucleoli and scanty cytoplasm. Indian file and targetoid patterns are noted (Fig 10)[64].

Dixan J M (1985) et al conducted receptor assay and revealed Estrogen, Progesterone receptor positivity in 67-92% of cancers[45] and E-Cadherin negativity[64].

TUBULAR CARCINOMA[64]:

This special type of tumour with a favourable prognosis shows well differentiated tubular elements with open lumen lined by a single layer of epithelial cells. These carcinomas measure between 0.2 cm- 2 cm in diameter. The significant feature is the presence of open angulated tubules having single layer of epithelial cells. Tubular carcinoma is always positive for hormone receptors (ER,

PR positive) and EGFR negative. Pure tubular carcinoma executes excellent long term prognosis.

INVASIVE CRIBRIFORM CARCINOMA (ICC):

This is an invasive tumour with good prognosis that grows in a cribriform pattern. ICC constitutes 0.8-3.5%. Microscopically, this tumour has well defined spaces formed by arches of cells (a sieve-like pattern) (Fig11). According to WHO, it shows estrogen receptor positivity in 100% and progesterone receptor positivity in 69% of cases[64].

MUCINOUS CARCINOMA:

In 1852, Robinson RR et al has emphasised about gelatinous carcinoma of breast. The incidence rate is 0.8-6%[64]. WHO classification describes: "large amount of extracellular mucin sufficient to be visible both macroscopically and microscopically around the tumour cells" [64]. (Fig 3,4).

Diab SG (1999)[9] in his study documented estrogen receptor positivity in 73-95%, progesterone receptor positivity in 79-84%. This tumour is negative for EGFR[64].

MEDULLARY CARCINOMA:

Geschicker CF (1945) et al documented that this high grade tumour as a different entity in breast carcinoma. Grossly, the tumour is well circumscribed and soft in consistency[53]. WHO describes medullary carcinoma as "well circumscribed carcinoma with poorly differentiated cells and scanty stroma showing lymphoplasmacytic infiltration"(Fig 12). In spite of the high grade of tumour, it carries good prognosis.[64]

Immunohistochemical studies revealed estrogen receptors are negative[64] with particular immunophenotype (i.e) p53 positive, HER-2/neu negative.[64]

PAPILLARY CARCINOMA:

Foote and Stewart (1946) et al described it as "A rare carcinoma whose invasive component particularly is in the form of papillary formations". Most of the previous literature about these tumours might include invasive and in situ papillary lesions. Invasive papillary carcinomas constitutes < 1-2% of invasive breast cancers, and have good prognosis. Fisher et al found out that invasive papillary carcinoma is macroscopically circumscribed in 2/3 of cases[64]. Delicate or blunt papillae lined by tumour cell is the microscopic feature (Fig 13). Estrogen, Progesterone receptor positivity is seen in 80% of these tumours.[59]

INVASIVE MICROPAPILLARY CARCINOMA: (Fig 14,15)

The term was defined by Siriaunkgul S and Tavassoli FA who first defined nine cases. WHO describes this as a tumour characterized by small groups of tumour cells seen within clear spaces in the stroma that looks like dilated vascular spaces. It constitutes less than 2% of all invasive breast cancers. Grossly it has lobulated outline because of expansive growth pattern. It is noted for its peritumoural angioinvasion seen in 60% of cases[64].

METAPLASTIC CARCINOMA: (Fig16)

In 1984, Kaufman M.W documented breast carcinoma with pseudosarcomatous metaplasia. These tumours constitute less than 1% of all invasive carcinomas[64]. The mean age at presentation is 55 years.

WHO 2003 publication describes this tumour as "a heterogeneous group of tumours with intimate admixture of adenocarcinomatous components with predominant mesenchymal differentiation".

Macroscopically, the tumours are firm and on cut surface it is solid with pearly white to glistening areas due to squamous or cartilaginous differentiation. In a study by Carter et al, immunohistochemical analysis revealed positivity for smooth muscle actin, cytokeratin 14, and p63 in 39% of cases. Oberman HA (1987) et al showed that the hormone receptors were negative[34].

PHYLLODES TUMOUR (PT): (Fig 20, 21)

Phyllodes tumours are biphasic tumours, with double layered epithelial component surrounded by an overgrowth of hypercellular mesenchymal areas typically seen in leaf-like structures[64].

Malignant phyllodes tumour (MPT) is a very rare breast malignancy and accounts for approximately 25% of all phyllodes tumours. This tumour metastasizes to lung, pleura and bone. Malignant phyllodes tumours with infiltrative margins are further classified into low-grade, and high-grade according to mitotic activity (with less or more than10 mitotic figures/HPF) and cellular atypia. Heterologous differentiation such as liposarcoma, osteosarcoma, chondrosarcoma or rhabdomyosarcoma can be seen[64]. Involvement of margins can be associated with local recurrences (frequency 27%).

PROGNOSTIC AND PREDICTIVE FACTORS[48]:

A prognostic factor is defined as a factor that is able to give information about the clinical course of the patient. They are the strongest predictors of death from breast carcinoma and are included in the American Joint Committee Cancer (AJCC) staging system. Predictive factors determine the likelihood of response to a particular therapy.

Invasive carcinoma or in situ tumour:

Invasive carcinomas metastasize locally or distantly at the time of diagnosis in contrast to in situ disease**.**

Distant metastases:

If distant metastasis is present, cure is unlikely and palliation can be achieved, for females with hormonally responsive tumors[53].

Tumour size:

The tumour size has a good association with the nodal status and survival rate. It is one of the best prognostic factors for predicting Disease free survival (DFS) and distant metastasis in stage I breast cancer[63]. Women with node negative carcinomas under 1 cm in diameter have a prognosis like that of females without breast cancer[44]. They have the 10-year survival rate of over 90%, whereas survival drops to 77% for cancer >2 cm [53].

Study by Gohari MR, et al., (2006) showed that patients with tumour size larger than 5 cm have higher chance of metastasis[16].

Lymph Node Stage:

Axillary lymph node status is the most significant prognostic variable for invasive tumours without distant metastasis.

The clinical assessment of nodal status is likely to give inaccurate results with both false positive [eg. palpable nodes without metastasis] and false negative findings [eg. small lymph nodes with metastatic deposits (Fig 9)][53]. Therefore, histopathological examination is required for accurate assessment (Susan C Lester, et al., 2004)[96]. Carter et al documented tumours having 4 or more axillary lymph nodes with metastasis usually have poorer survival regardless of tumour size.

Fisher ER, et al., (1993) emphasised that the number of nodes with metastatic deposits has prognostic significance; patients with 4 or more involved nodes have a worse clinical outcome than with <4 involved nodes[44]. As a prognostic parameter, the best grouping is as follows (Rosai and Ackerman's Surgical Pathology, 2004)[44].

1 – Negative nodes.

2 – One to three positive nodes.

3 – Four or more positive nodes.

Histological type:

Most poorly differentiated carcinomas have worse prognosis than their differentiated counterparts. Among special types, pure mucinous, tubular, and papillary carcinomas have good prognosis with more than 95% 5-year survival.

The typical medullary carcinoma had a particularly favourable outcome with a 92% 10-year survival. Histological type of carcinoma comparatively to grade has less importance for prognostication. So Pinder et al says that tumours should be typed and assigned grade to predict the choice of optimum treatment for breast carcinoma[37].

Excision Margins:

It is the most important contributions in the management of breast cancer. Microscopic examination of the margin status is usually performed to find out the adequacy of surgical excision and the frequency of recurrence. The excision margins are usually marked with India ink. Schnitt SJ et al., (1994) in their study defined that margin is positive when the tumour is present at the inked margin, a close margin when tumour is present and negative margin when no tumour is present within one mm of the inked margin. It is emphasised that 5 year recurrence rate for those with negative, close, focally positive and more than focally positive margins were 0%, 4%, 6% and 21% respectively[49].

Vascular Invasion:

Penetration of small lymphatic and blood vessels has relationship with metastasis and a poorer prognosis. It is difficult to delineate true vessels from

artifactual spaces (Ellis IO, et al., 1996)[55]. Vascular invasion should be searched for, in the peritumoral area and it must have an endothelial lining [55,63].

Reticulin stain, endothelial markers (CD 31 and CD 34) can be used for confirmation. Most of the previous reports are documenting that there is significant association between the vascular invasion and local recurrence, disease-free survival or overall survival (Pinder S, et al 1995)[38].

Histological grade:

Greenhough RB (1925)[18] et al was the first to assess the histological grade in breast cancer by assessing eight different morphological factors - the amount of gland formation, the presence of secretory vacuoles, cell size, nuclear size, variation in the size of both cells and nuclei, the degree of nuclear hyperchromatism and the number of mitosis. Patey and Scarff RW., et al (1928) highlighted on the amount of tubule formation, nuclear atypia and hyperchromatism. The mitotic figures were identified to be of less significance by them.

In 1957, Bloom HJG, a radiotherapist and Richardson, a surgical researcher have come up with a numerical scoring system; the three factors-tubule formation, nuclear morphology and mitosis, was scored each on a figure of 1 to 3, giving a score of 3 to 9 points[5]. This Patey and Scarff method, modified by Bloom and

Richardson was preferred as the grading system by the WHO (Ellis IO, et al., 1992)[64]. Black MM, et al., (1955) re-studied the method advocated by Bloom (1950) and end up that nuclear morphology was most significant. Since both architecture (Bloom – Richardson system) and cell morphology (Black) have been associated with prognosis, they have been used together (Lash RH, et al., 1986). Elston has been the leader of this grading system, which is now termed as the Nottingham modification of the Scarff Bloom - Richardson System (SBR)[55].

The grading criteria for this system are:

i) Tubule formation:

Only structures with a clearly defined lumen, indicative of ductal or glandular differentiation are included. Spaces formed as a consequence of other mechanism, such as shrinkage artefact or cellular necrosis is excluded[55].

ii) Nuclear pleomorphism:

In order to introduce a degree of objectivity, the size and shape of normal epithelial cells present in breast tissues adjacent to the tumour should be used as a reference point. If normal epithelial structures are not present in the tumour section, then it is usually possible to find inflammatory cells such as lymphocytes for comparative purpose. Allowance should be made for the fact that lymphoid cells have a relatively smaller overall size than epithelial cells[55].

iii) Mitotic counts:

Most significant modification in SBR method has been made by Ellis in the assessment of mitotic counts. Hyperchromatic nuclei is more likely to indicate individual cell necrosis than proliferation, and such nuclei should be excluded from the counts. Only figures which legibly accomplish and satisfy the morphological criteria for the different stages of mitosis - prophase, metaphase, anaphase and telophase are included in the count (Elston CW, et al., 1998)[55].

A minimum of 10 microscopic fields is counted at the tumour periphery where there is more proliferative activity (Verhoeven D, et al., 1990)[55]. Allocation of points is shown in the table[64]:

Feature	Score
Tubule and gland formation	
Majority of tumour (>75%)	1
Moderate degree (10-75%)	2
Little or none (<10%)	3
Nuclear pleomorphism	
Small, regular uniform cells	1
Moderate increase in size and variability	2
Marked variation	3
Mitotic counts	
Dependent on microscope field area	1-3

Examples of assignment of points for mitotic counts for three different field areas:			
Field diameter (mm)	0.44	0.59	0.63
Field area (mm^2)	0.152	0.274	0.312
Mitotic count*			
1 point	0-5	0-9	0-11
2 points	6-10	10-19	12-22
3 points	>11	>20	>23

The comprehensive grade of the tumour is acquired by adding the scores for each factor giving a sum of 3 – 9 points.

Points allocated for overall grade of the tumour:

3 - 5 – Grade I (Fig17).

6 - 7 – Grade II (Fig 18).

8 - 9 – Grade III (Fig 19).

Significance of Grading:

The degree of differentiation in carcinoma of the breast is revealed in the histological appearance of the tumour and this feature forms the basis for the grading system[5]. Bloom and Richardson in his study of 1409 cases of breast cancers with 15 years follow up found that grading identified the malignant potential of the tumour. The real value of histological grading is in assessing the frequency of metastases and death.

Multiple independent studies have shown that Nottingham grading system is equivalent to the lymph node status and more than that of tumour size in assessing the prognosis. Rakha et al found that high-grade tumours, with their risk of early recurrence and death need prompt use of adjuvant chemotherapy and grade 1 tumours can be given long-term follow-up with or without less toxic systemic therapy[40].

Histologic grading should be done in every case of invasive carcinoma of breast. But some special types such as tubular, invasive cribriform and mucinous carcinoma by typing itself are comparable with the grade I status[55], Classical Infiltrating lobular carcinoma are designated as grade 2[40]. Medullary carcinomas are considered as grade 3 but have been found to have good outcome and grading

is less significant. In most of the special types, the grade does not represent a prognostic factor[9].

Assessment of prognostic factors by multiple regression technique of Cox documented that only tumour size, histological lymph node status and histological grade have association with overall survival. Based on the coefficient of significance produced in the Cox analysis, a simple prognostic index has been formulated as follows[55]:

NPI = 0.2 x tumour size + lymph node (1-3) stage + histological grade (1-3). The higher the value for NPI, the worse the prognosis. Three groups have been divided by devising cut off points.

<3.4 - Good prognostic group (GPG).

3.41-5.4 - Moderate group (MPG).

>5.4 - Poor group (PPG)[55].

Thus grading seems to be meaningful in "Not otherwise specified" ductal carcinomas which account for more than 80 % of the breast cancers.

HORMONE RECEPTORS:

Over a hundred years ago, the hormone receptor sensitivity of breast carcinoma has been reported. Albert Schinzinger was the first surgeon who

proposed that surgical oophorectomy can be offered as a treatment for breast cancers in 1889. It took another sixty years for Etwood jenson and colleagues to discern an estrogen binding protein which is now called as the "Estrogen Receptor". Exogenous estrogenic harmones could have an effect upon the proliferation of tumour cells has been observed by Haddow et al[19] in 1940. Hence, he has laid the importance of non surgical endocrine therapy.

Hormonal agents that is used for therapy can be classified in to three major categories. They are gonadotrophin releasing hormone agonist and aromatase inhibitors. Tamoxifen that belongs to third category is nowadays the most commonly used agent which acts locally by restraining the action of hormones on the target tissues.

Later on, Horwitz et al found that the status of progesterone receptor, a protein induced by the estrogen can make beneficial addition to the prognostic value afforded by estrogen receptor alone.

ER, PR AS PROGNOSTIC AND PREDICTIVE FACTOR:

The status of estrogen and progesterone receptors in an invasive malignant tumour of breast can play the role of both prognostic and predictive factor[41].

As a prognostic factor, ER and/or PR positivity can be correlated with decreased death rate and an improved survival when compared with ER, PR

negative tumours[35]. It has been documented that 5-year overall survival is 83% in ER+/PR+ patients but it is reduced to 69% in the receptor negative individuals.

The NSABP B-06 trial (National Surgical Adjuvant Breast and Bowel Project data) that has been carried out with early-stage breast cancer revealed that ER-positive patients had an improved 5-year Disease free survival (DFS) and overall survival (OS) of 74% and 92% respectively but this has been drastically reduced to 66% and 82% respectively in hormone receptor negative status[41].

Analysis of steroid hormone receptor status is a very precise tool that can indicate in advance the probability of usefulness of tamoxifen. The recently organised randomized trials with the application of tamoxifen as adjunct therapy in 37,000 females who were affected with breast cancer[58] illustrated that the same drug administered for 5 years end up with the outcome of relative decrease in the recurrence rate of 47% and mortality rate of 26% in individuals having steroid receptor positive cancers. When patients were treated with tamoxifen for five years, it reduced the probability of developing tumour in the opposite breast by 47%[41]. It was not beneficial to the women with the receptor-negative tumours[58].

Jamil et al advocated hormonal therapy and chemotherapy preferentially to females who have attained menopause and showed that patients with ER+/PR- and ER-/PR- status who were offered the drugs responded well compared to premenopausal females[26].

ER, PR - AS BASIS FOR RESPONSE TO HORMONAL THERAPY:

The importance of the study of hormone receptor status lies in the selection of individualised treatment strategy for breast cancer subtypes[26]. Clinically, the positive status can state in advance about the likelihood of response to drugs like selective estrogen receptor modulators and whether or not the patient will respond to hormone therapy.

Recent advances in the characterization of different breast cancer types have intensified our focus on the discovery of druggable targets for the development of more selective breast cancer treatments.

Breast cancer-related deaths have markedly decreased with the discovery of endocrine agents (e.g. tamoxifen and aromatase inhibitors) that selectively target ER expressing breast tumours. This serves as a motivation to continue to define potential druggable targets for hormone receptor and HER2 negative (triple-negative) breast cancers that do not respond to endocrine therapies or to trastuzumab and for which cytotoxic chemotherapy is the only systemic treatment option. In-depth characterization of breast tumours is imperative for the development of targeted therapies.

Hormone receptor status as determined by immunohistochemistry correlated with therapy regimens like chemotherapy and hormone therapy[26].

The Immunohistochemistry assay has substituted the older methods like ligand binding assay and is nowadays preferred as the mode of choice for analysing the hormone receptors. It estimates the proportion of cancer cells expressing the positivity.

To a greater extent, there is a notification that variations in the procedures and techniques of the assay used could make alterations in the results and interpretations. The changes can also be due to the study group of patients with distinct and modified clinical stages and aggressive phenotypes of carcinomas[43].

The outcome will also be influenced by inadequate fixation. So the specimens should be obtained immediately after the surgical procedures. The commonly used fixatives are formal-saline and neutral buffered formalin. The fixation should be quick and the fixative should be evenly distributed throughout the specimen[41].

A hybrid block which encompasses distinct tissues containing areas abundant with receptors admixed with receptor deplete and negative tissues should be used. It is likely that the tumour tissues that should be evaluated possess normal appreciable breast parenchyma to serve the purpose of positive internal control. The process should be repeated when difficulties are encountered in the staining of normal parenchymal tissue.

The type and grade of the tumour should also be considered so that they both have been proved to have impact on the interpretation of inferences. This is supported by the fact that the tumours that are well differentiated are highly improbable to yield negative results[41].

Scoring system:

Various respective scoring methods have been imparted in the literature. The positivity should be depicted by taking in to account the staining in the nuclei of the tumour cell. It is important to estimate the entire invasive element of the tumour.

The importance of establishing a definite scoring system is to make certain that homogeneity should exist between various laboratories. On considering this issue retrospectively, it is essential to bring emphasis to Allred score assigned by Craig Allred few years ago. In 2010, Asim et al added an adjunct for the widespread use of this method nowadays and supplemented by the study report that the sensitivity as well as the specificity of the Allred score was very high in contrast to other methods[1]. The score is allocated by the estimation of two scores, first is the proportion score from 0 to 1, given by analysing the percentage of nuclei in the cells, having taken the stain and secondly, the intensity score from 0

to 1 given by exploring the strength and magnitude of staining as negative, weak, average and intense.

Both the scores are added to give the total score.

Various rational motives for identifying both the hormone receptor positivity and analysing the intensity of the reaction of breast carcinomas are as follows:

1. Several reviewed facts and materials about the evaluation of both receptors are accounted to the management of carcinomas with metastasis in the view of, greater the percentage and intensity of positivity of tumour cells, then higher the possibility of better outcome and effects to endocrine therapy[41].

2. Virtually, there would not be any anticipation of response in individuals with breast carcinomas which do not exhibit the staining pattern.

3. The consideration of progesterone receptor along with estrogen receptor is ideal and worth. The tumours that have very low ER positivity but high PR positivity could still respond to hormonal treatment is the contributory evidence provided by the progesterone receptor.

4. Even though the degree of staining is low in the tumours scoring 2 or less than 2, the adjuvant endocrine therapy has been proved beneficial in those patients too. This highlights and foregrounds that it is necessary to develop sensitive and

standardised procedures which have the ability to trace out these low receptor levels.[41]

From then until now, after the invention of ER and later progesterone receptor (PR), vigorous and innovative efforts has been made on the relevance and importance of hormone receptors in breast cancer evolution, progression, metastasis, prevention and the management of Breast cancer.

MATERIALS AND METHODS

The study group comprised of malignant breast lesions received in the Department of Pathology, Madurai Medical College, Madurai from the Government Rajaji hospital, Madurai during the period of July 2010 to June 2012.

During the study period, 151 trucut biopsies, 313 lumpectomies and 215 mastectomy specimens were received. Out of these, 74 trucut biopsies, 37 lumpectomies and 157 mastectomy cases were proved to be malignant. 41 trucut biopsies and 22 lumpectomy cases were followed by mastectomy. Out of the 157 mastectomy specimens, 154 cases were malignant epithelial lesions and 3 cases were malignant phylloides tumour. This study group consisted of 157 cases of malignant breast lesions surgically treated by mastectomy.

Detailed clinical history of these 157 cases such as age, sex, menopausal status, laterality of the lesion, nipple discharge and clinical diagnosis were recorded in the proforma and tabulated in the master chart. (Annexure I and V)

Mastectomy specimens were bisected and fixed in 10% formalin for 24 – 48 hours. Detailed gross examination pertaining to side and type of mastectomy, list of structures included in the specimen like skin, nipple, major and minor pectoralis muscles, fascia, axillary tissue, chest wall structures, weight, overall size of the specimen, dimensions of the skin, features of external appearance such as

- shape and colour of skin
- location and extent of skin changes (scars, recent surgical incisions, erythema, oedema, flattening, retraction and ulceration)
- appearance of nipple and areola (erosions, ulceration, retraction, inversion) were noted.

They were cut at 1cm interval with special attention to include base, lateral margins, skin and ulcerated areas. On cut section, location of lesion, distance from the nipple and skin, tumour size, shape, consistency, colour, presence of necrosis, haemorrhage, calcification, attachment to skin, muscle, fascia or nipple and distance from cut margins, lymph nodes if present, number of nodes in each group (low, mid, apical axilla) and size of the largest node in each group were noted.

The representative sections were taken from the tumour, nipple, pectoralis major muscle (in radical mastectomies), lateral and posterior surgical margins and palpable lymph nodes.

The tissue slices were processed in various grades of alcohol and xylol and subsequently embedded in paraffin wax. Paraffin sections of 4 μm thickness were subjected to haematoxylin and eosin staining.

They were analysed for the tumour size, tumour grade, vascular and perineural invasion and pTNM classification was done.

Histological assessment of tumour grade is done by Modified Richardson – Bloom Scoring system for 144 malignant epithelial lesions. Nodal status and margins involvement were recorded for all the cases.

IMMUNOHISTOCHEMICAL ANALYSIS OF HORMONE RECEPTORS:

Immunohistochemical analysis of hormone receptor assay was done for selective cases. It was done in paraffin embedded tissue blocks, by using the Supersensitive Polymer HRP system based on non-biotin polymeric technology that makes use of two major components, Super enhancer and poly- HRP reagent.

The retrieved antigen was bound to primary antibody and then detected by the addition of secondary antibody conjugated with horse radish peroxidase polymer and DAB substrate. The score was calculated after adequate colour development which can be more readily visualized under a light microscope.

The step by step procedure is included in Annexure III.

OBSERVATIONS AND RESULTS

In the two year study period from June 2010 – July 2012, there were 20,367 specimens received in the department of pathology, Madurai medical college, Madurai. Of these, the breast lesions accounted for 679 cases. During this study period, benign tumours were 261 cases (48.97%) and malignant tumours were 272 cases (51.03%).

This prospective study of breast neoplasms covered a total of 157 malignant breast lesions that were treated by mastectomy in Government Rajaji hospital, Madurai. This included the malignant epithelial and mesenchymal tumours, so the overall incidence is found to be 23.12%.

Age distribution of malignant breast tumours:

CHART 1:

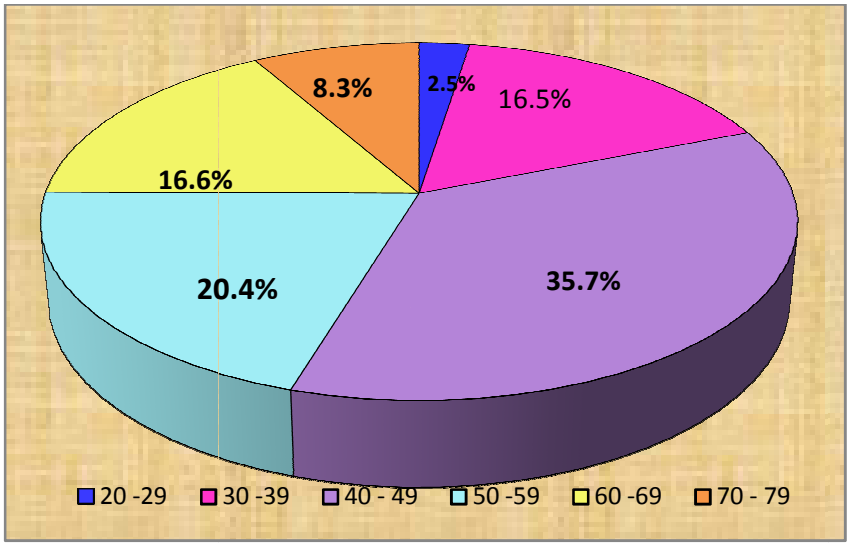


Table 1 and Chart 1 shows the distribution of malignant breast tumours according to age. 4 cases were seen in 20 - 29 year age group (2.5%), 26 cases were seen in 30 - 39 year age group (16.5%). Malignant tumours had a peak incidence in the age group of 40-49 years (35.7%), followed by 50- 59 years (20.4%). 26 cases were seen in 60 – 69 year age group (16.6%) and 13 cases were seen in the 70 - 79 year age group (8.3%). The mean age of malignant breast tumours observed in our study is 49.5 years.

TABLE 1:

Age group	**Malignant breast tumours**	
	No	**%**
20-29 years	4	2.5
30-39 years	26	16.5
40-49 years	56	35.7
50-59 years	32	20.4
60-69 years	26	16.6
70 & above	13	8.3
Total	157	100
Range	24-79 years	
Mean	49.5 years	

S.D	11.9 years

Sex incidence:

All of the cases in our study who were surgically treated with mastectomy were females whereas the breast malignancies can occur in male breast also.

CLINICAL FINDINGS:

Incidence according to Menopausal status:

In the present study, we have made a categorisation with regard to the attainment of menopause. 49 years has been taken as the outermost cut off point for premenopausal group. This has been preferred to make apparent that most of the women who had cyclical menstrual cycles were < 49 years, while at the same time older females >49 years had no menstruation or had occasional cycles.

TABLE 2:

Menopausal status	**No of cases**	**Percentage (%)**
Premenopausal	86	54.78%
Postmenopausal	71	45.22%
	157	100

Table 2 indicates 86 patients in our study were in the premenopausal age group (54.58%) and 71 cases were in the postmenopausal age group (45.22%).

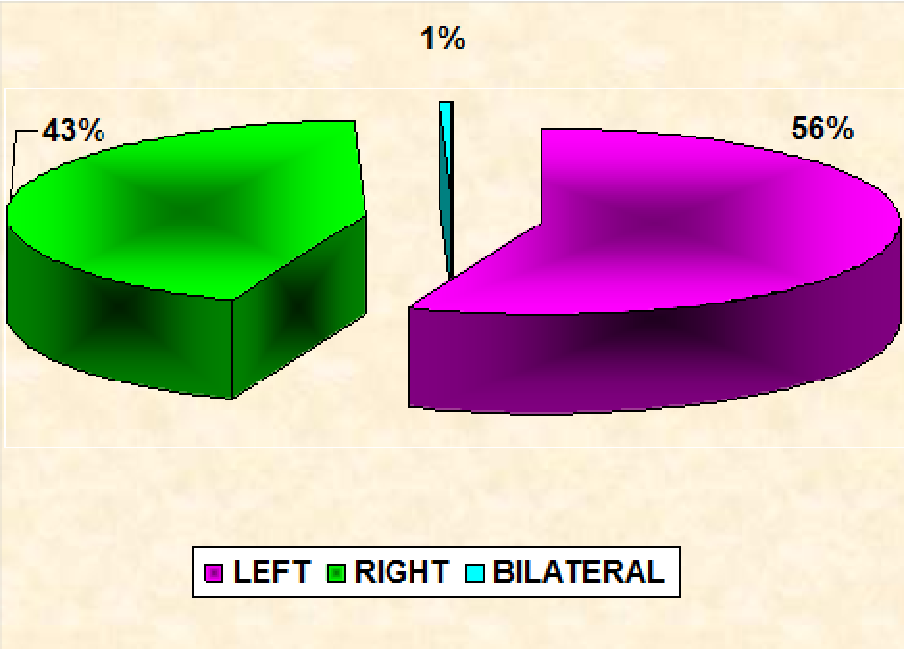
Laterality of malignant breast tumours:

TABLE 3:

Side	**No of Cases**	
	No	**%**
Left side	88	56.1
Right side	68	43.3
Bilateral	1	0.6
Total	157	100

From the table 3 and chart 2, it is evident that maximum number of cases had left sided breast tumours (56.1%) and 68 cases had right sided breast tumours (43.3%). Bilateral lesions comprised only 0.6% (1 case).

CHART 2:



Percentage of quadrant involved:

TABLE 4:

S.no	**Quadrant**	**No of cases**	**Percentage (%)**
1.	Upper outer	75	47.77%
2.	Lower outer	24	15.29%
3.	Upper inner	21	13.37%
4.	Lower inner	10	6.37%
5.	Subareolar / central	27	17.20%
	Total	157	100

Table 4 reveals that in the present study, 47.77% of cases presented with lump in the upper outer quadrant, followed by subareolar region (17.20%) and lower outer quadrant (15.29%). Other quadrants involved were upper inner (13.37%) and lower inner (6.37%). 15 cases showed involvement in two quadrants and 10 cases in all the quadrants. 25.47% (40/157) of cases presented with nipple discharge.

Size of the tumour:

TABLE 5:

S.no	**Tumour size**	**No of cases**	**Percentage (%)**
1.	≤ 2 cm T1	26	16.56
2.	2-5 cm T2	56	35.67
3.	≥ 5 cm T3	68	43.31
4.	Skin or chest wall T4	7	4.46
	Total cases	157 cases	100%

Table 5 shows 26 cases had tumours ≤ 2 cm (16.56%), 56 cases had tumours with size 2-5 cm (35.67%) and most of the tumours (68 cases) had ≥ 5 cm tumour size (43.31%). 7 cases had tumours with involvement of skin (4.46%).

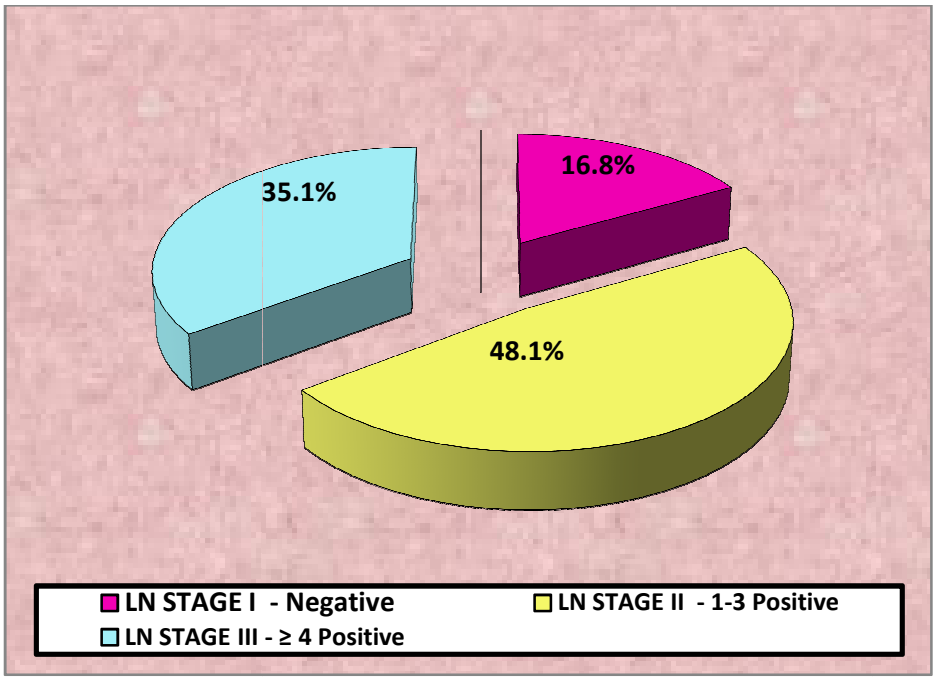
Axillary Lymph Node Status for Invasive Epithelial Tumours:

TABLE 6:

Lymph Node Stage	**No of Cases**	**Percentage**
Stage I (negative)	26	16.8%
Stage II (1-3 positive)	74	48.1%
Stage III (≥ 4 positive)	54	35.1%
Total cases	154 cases	100%

Table 6 and Chart 3 shows the percentage of cases in each lymph node stage. 16.88% cases were of lymph node stage I, 48.1% cases have 1-3 positive lymph nodes and 35.1% of cases have 4 or more than 4 positive lymph nodes (stage III lymph node status).

CHART 3:



Distant metastasis:

In the present study, none of the patients presented with metastasis to distant organs.

TNM staging of malignant epithelial tumours of the breast:

CHART 4:

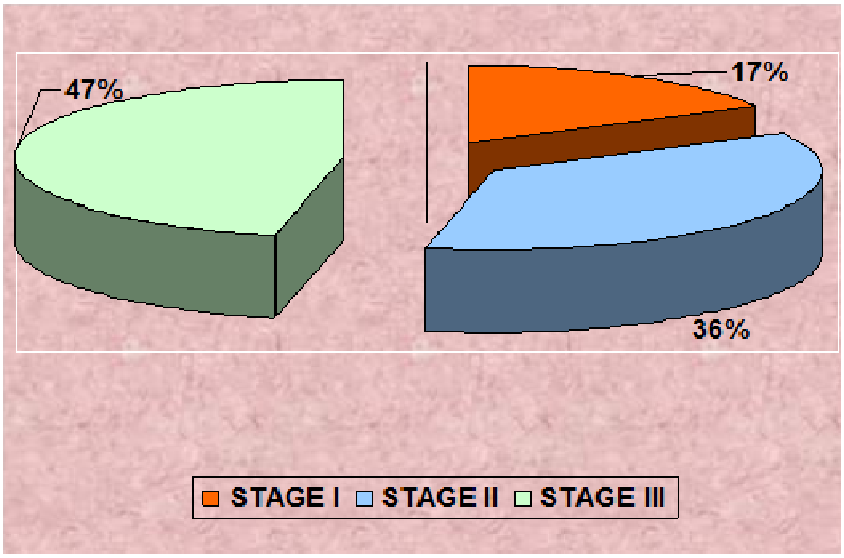


Table 7 and chart 4 shows the percentage of cases in each stage in our study. 26 cases were seen in stage I (16.88%), 56 cases were seen in stage II (36.37%) Maximum number of 72 cases (46.75%) were seen in stage III.

TABLE 7:

S.no	**Stage**	**No Of Cases**	**Percentage (%)**
1.	Stage I	26	16.88%
2.	Stage II	56	36.37%
3.	Stage III	72	46.75%
	Total cases	154	100%

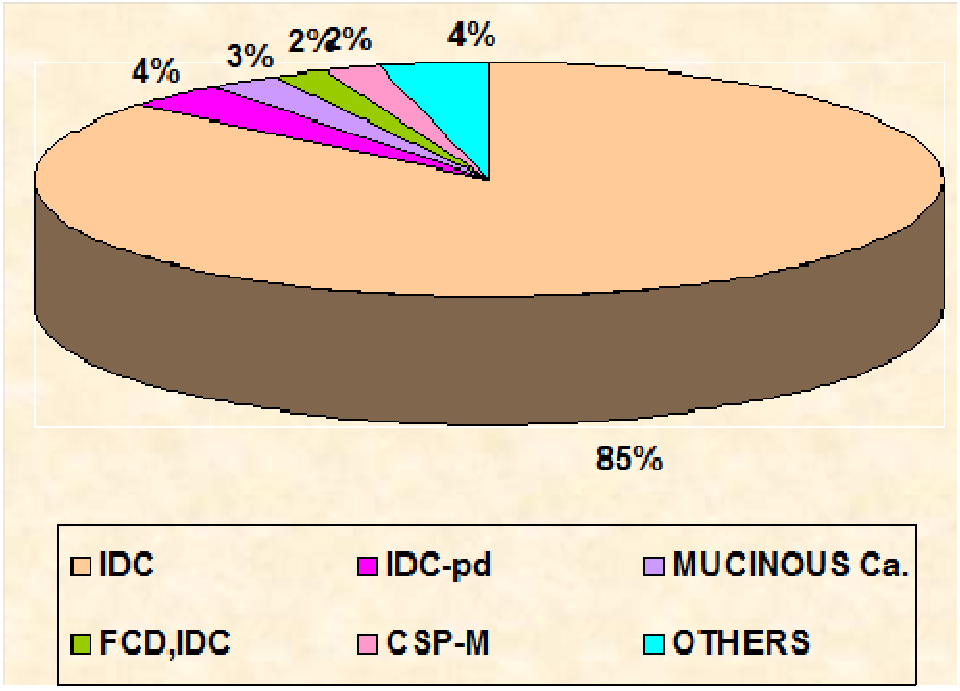
DISTRIBUTION OF HISTOLOGICAL VARIANTS OF BREAST CARCINOMAS AND MALIGNANT PHYLLOIDES TUMOUR:

TABLE 8:

S.no	Histological variants	No of cases	Percentage (%)
1.	Invasive ductal carcinoma NOS type	138	87.89%
2.	Paget' disease with IDC-NOS type	6	3.82%
3.	Invasive lobular carcinoma	1	0.64%
4.	Mucinous carcinoma	4	2.54%
5.	Invasive cribriform carcinoma	1	0.64%
6.	Papillary carcinoma	1	0.64%
7.	Micro Papillary carcinoma	1	0.64%
8.	Medullary carcinoma	1	0.64%
9	Metaplastic carcinoma	1	0.64%
10.	Malignant phylloides tumour	3	1.91%
	Total cases	157	100%

Table 8 and Chart 5 shows the distribution of histological variants in breast carcinoma and the malignant mesenchymal lesions. Among the 157 cases, 138 cases (87.89%) were Invasive Ductal Carcinoma NOS type. 6 cases were associated with Paget's disease (3.82%), 4 cases (2.54%) were Mucinous carcinoma and one each (0.64%) in other special sub-types including Lobular carcinoma, Cribriform carcinoma, Papillary carcinoma, Micropapillary, Metaplastic and Medullary carcinoma. 3 cases were Malignant phylloides tumour (1.91%).

CHART 5:



HISTOLOGICAL GRADE IN INVASIVE DUCTAL CARCINOMA NOS TYPE:

Histological grading is done in breast carcinomas according to Modified Bloom-Richardson grading system (SBR).

Only 144 cases which were invasive ductal carcinoma NOS type were included for grading because invasive tumour that belongs to special histological types have a predefined grade as follows.

e.g. Tubular carcinomas are grade 1,

Classic Lobular carcinomas are always grade 2 and

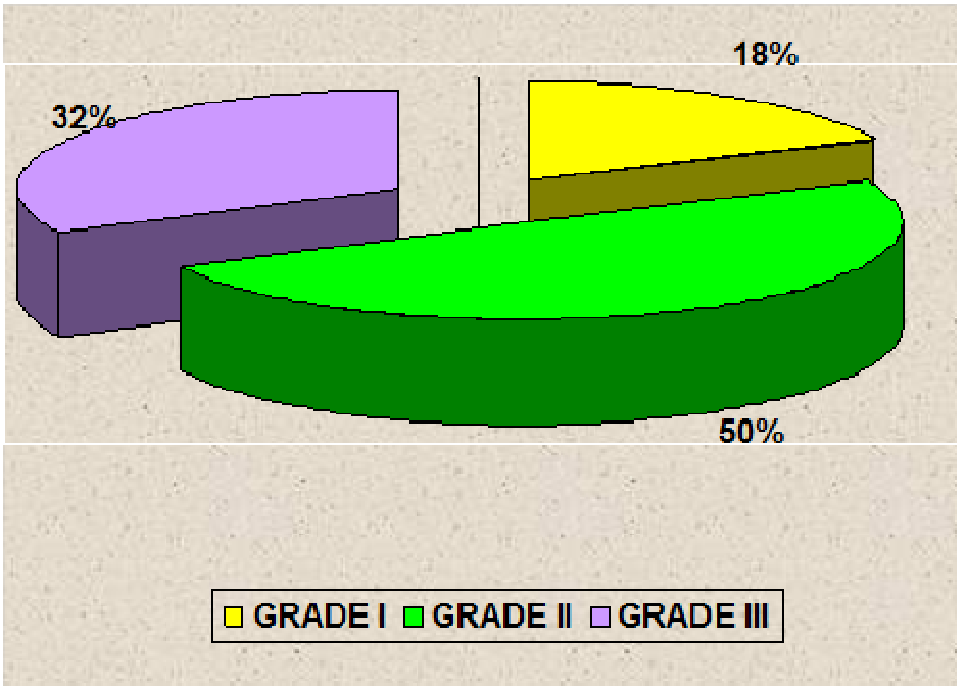
Medullary carcinomas are grade 3 respectively.

Table 9 and Chart 6 shows that out of 144 cases of Invasive ductal carcinomas, not otherwise specified type (IDC - NOS type), 26 cases (18.05%) were seen in grade I, 72 cases (50%) were in grade II and 46 cases (31.95%) were in grade III**.** So in the present study maximum number of cases were seen in grade II (50%).

TABLE 9:

S.no	Histological grade	No of cases	Percentage (%)
1.	Grade I	26	18.05%
2.	Grade II	72	50%
3.	Grade III	46	31.95%
	Total cases	144 cases	100%

CHART 6:



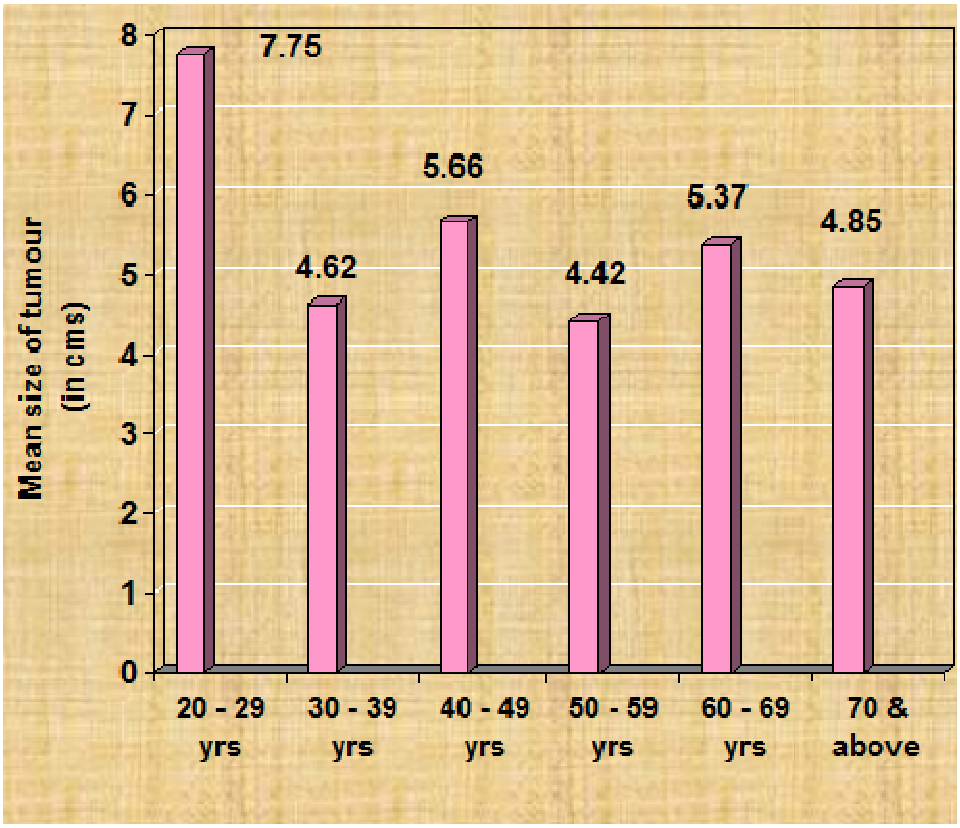
RELATIONSHIP BETWEEN AGE AND OTHER CHARACTERISTICS OF MALIGNANT TUMOURS:

TABLE 10: Age and size of tumour:

Age group	**Size in cms**					
	T1<2cm	**T2 2-5cm**	**T3>5cm**	**T4skin or chest**	**Mean**	**SD**
20-29	-	1	3	-	7.75	2.87
30-39	7	12	7	-	4.62	3.18
40-49	5	17	28	4	5.66	2.49
50-59	9	13	10	-	4.42	1.9
60-69	2	11	11	2	5.37	2.27
70 & above	3	2	6	1	4.85	2.12
Total	26	56	65	7		
'P' value - 0.0378 (Significant)						

Table 10 and Chart 7 indicates that maximum number of cases, 17 and 28 cases respectively in T3 and T4 tumour size is seen in the 40-49 years age group. Maximum mean size (7.75cm) is seen in the younger age group 20-28 years. The mean tumour size in 30 - 39 year age group is 4.62 cm, 40 – 49 year age group is 5.66 cm, 50 – 59 year age group is 4.42cm, 60 -69 year age group is 5.37 cm, 70 – 79 year age group is 4.85 cm. The relationship between age and the mean size of the tumour is statistically significant with P value (0.0378).

CHART 7:



CORRELATION OF AGE WITH OTHER PROGNOSTIC PARAMETERS:

TABLE 11:

AGE GROUP	GRADE			TNM STAGE			NODAL STATUS		
	I	**II**	**III**	**I**	**II**	**III**	**Neg**	**1-3**	**>4**
20-29	-	2	2	-	1	3	-	1	3
30-39	7	12	7	7	12	7	7	12	7
40-49	5	28	17	5	17	32	5	29	20
50-59	9	12	9	9	13	10	9	11	12
60-69	2	15	7	2	11	13	2	16	8
70-79	3	3	4	3	2	7	3	5	4
TOTAL	26	72	46	26	56	72	26	74	54

Table 11 indicates Maximum number of cases in grade I (9 cases) were in the age group of 50- 59 years. Out of the 4 cases in 20-29 year age group, 3 cases were in stage III. Maximum number of cases in grade III (17 cases), stage III (32

cases) and nodal status with 1-3 positive lymph nodes (29 cases) and >4 positive lymph nodes (20 cases) fall in the age group 40- 49 years.

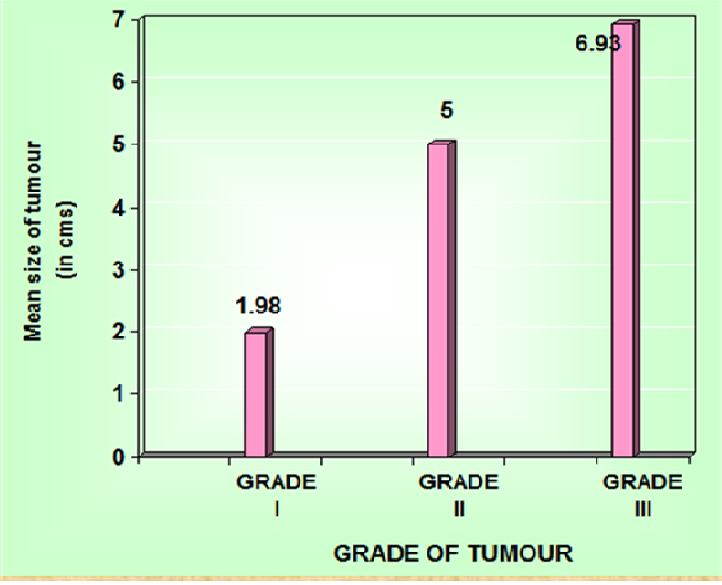
CORRELATION BETWEEN HISTOLOGICAL GRADE OF TUMOUR AND OTHER FACTORS:

TABLE 12: Histological grade of Tumours and size of tumour:

Grade of tumour	**Size of tumour (in cms)**	
	Mean	**SD**
Grade I	1.98	0.1
Grade II	5.0	1.91
Grade III	6.93	2.22
'p'	**0.0001 (Significant)**	

Table 12 and chart 8 shows maximum mean tumour size (6.93cm) was observed in high grade (grade III) tumours with significant statistical correlation with P value of 0.0001.

CHART 8:



CORRELATION OF HISTOLOGICAL GRADING WITH TNM STAGE:

TABLE 13:

S.no	Stage	Histological Grading					
		Grade I		Grade II		Grade III	
		No	%	No	%	No	%
1.	Stage I	26	100%	-	-	-	-
2.	Stage II	-		46	92%	4	8%
3.	Stage III	-		26	38.24%	42	61.76%

Table 13 shows the correlation between TNM staging and modified Bloom and Richardson (Nottingham) grading. All of the cases of stage I disease were of grade I (100%). Among stage II cases, 92% were of grade II and 8 % were of grade III. Among the stage III cases, 42 cases (61.76%) were of grade III and 26 cases (38.24%) were of grade II.

CORRELATION OF HISTOLOGICAL GRADE AND AXILLARY LYMPH NODE STATUS:

Table 14:

S.no	**Lymph node stage**	**Histological Grading**					
		Grade I		**Grade II**		**Grade III**	
		No	**%**	**No**	**%**	**No**	**%**
1	Stage I	26	100%	-	-	-	-
2	Stage II	-		55	83.33%	12	16.67%
3	Stage III	-		17	32.69%	35	67.31%

Table 14 shows the correlation between axillary nodal status and histological grade. All of the grade I cases were of lymph node stage I (100%). 83.33% of cases with 1-3 positive nodes were of grade II. Among grade III cases, 35 cases had 4 or more positive lymph nodes (67.31%) and 17 cases (32.69%) had 1-3 positive lymph nodes (LN stage II).

CORRELATIVE STUDY OF HORMONE RECEPTOR STATUS IN BREAST CARCINOMAS:

In the present work, the study of hormone receptor (ER, PR) status has been undertaken in 20 cases of IDC – NOS type. This included cases in each age group. The results are shown below.

TABLE 15: ER status in relation to age groups (n=20):

Age group	Total no of cases	No of ER+ cases	No of ER- cases
20-29	2	0	2
30-39	2	1	1
40-49	6	4	2
50-59	6	5	1
60-69	3	2	1
70-79	1	1	0
Total	20(100%)	13(65%)	7(35%)

TABLE 16: PR status in relation to age groups (n=20):

Age group	Total no of cases	No of PR+ cases	No of PR- cases
20-29	2	0	2
30-39	2	0	2
40-49	6	2	4
50-59	6	2	4
60-69	3	1	2
70-79	1	0	1
Total	20	5(25%)	15(75%)

Table 15 and 16 shows the ER/PR status in correlation with different age groups. It was observed that in the total 13 ER positive cases and total 5 PR positive cases, majority of the cases were observed in the age group of 50-59 years and 40-49 years, but the ER positivity was higher in the age group 50-59 years compared with the age group of 40-49 years.

In the age group of 50-59 years, 83.33% (5 of 6 cases) were positive for ER and 2 of 6 cases (33.33%) were positive for PR. The percentage was found to be 66.66% (4 of 6) for ER positive cases and 33.33 % (2 of 6) for PR positive cases in the age group of 40-49 years. There were 2 cases in age group 20 – 29 years, 1 case in 30-39 years age group, 1 case in 60 – 69 age group respectively were negative for ER.

HORMONE RECEPTOR STUDIES IN CORRELATION WITH MENOPAUSE:

ER, PR hormone receptor study by immunohistochemistry was done for 10 patients of the premenopausal age group and 10 patients of the postmenopausal age group with IDC NOS type and the results are shown below:

TABLE 17:

Hormone receptor study in correlation with menopause:

ER/PR STATUS	**Premenopausal (n=10)**	**Postmenopausal(n=10)**
ER+, PR+	2(20%)	3(30%)
ER+, PR-	3(30%)	5(50%)
ER-, PR-	5(50%)	2(20%)

From the table 17 showing the correlation of menopausal status with ER and PR status, it is evident that the hormonal positivity was greater in postmenopausal (30%) cases than that in premenopausal cases (20%). ER positivity was 80% (8 of 10 total postmenopausal cases) in postmenopausal period and 50% (5 of total 10 premenopausal cases) in premenopausal period. PR positivity was 30 % (3 of 10 total postmenopausal cases) in postmenopausal period which was higher than 20% (2 of total 10 premenopausal cases) in premenopausal patients.

In a total 13 ER positive cases, 61.54% (8 of 13 total positive cases) was observed in postmenopausal period and 38.46% (5 of 13 total positive cases) was observed in premenopausal period. In a total of 5 PR positive cases, 60% (3 of 5 total positive cases) was observed in postmenopausal period and 40% (2 of 5 total positive cases) was observed in premenopausal period. The overall percentage of

the receptor status of the patients showed that estrogen receptor positive and progesterone receptor negative tumours (ER+ and PR-) were highest in postmenopausal patients in the study group (50%). In the premenopausal group of patients, ER- PR - tumours were the highest which constitutes 50% whereas ER+ PR + tumours constitute only 20%.

ER, PR study in different histological types of breast cancers:

In correlating the ER, PR status with different histological types of breast cancers, one case of Papillary carcinoma was positive for both ER and PR. One case of Infiltrating lobular carcinoma was positive for ER and focally positive for PR. One case of Mucinous carcinoma was positive for ER but negative for PR. One case each of Metaplastic carcinoma and Medullary carcinoma in the present study is negative for ER and PR.

DISCUSSION

Breast is one of the commonest sites of primary neoplasms as it is influenced by the action of hormones. It stands as the second common cancer among south Indian females[6,31]. In an overview, one lakh patients are annually diagnosed with breast cancer in India. In accordance with the ICMR-PBCR data, breast cancer comprises > 30% of all cancers and more prevalent in urban women[31]. In the rural areas, after the cervical cancer, breast cancer is the second most common cancer in females.

There appears to be a wide variation in incidence between countries, and also within any country and this variation in incidence may be because of more widespread screening programmes and alterations in the registration procedures in certain countries, but there appears to be a real and genuine increase in the incidence not accounted for by these factors [2]. This highlights the importance of early diagnosis and appropriate management in our country.

Pathology has performed the "gold standard" role in diagnosing breast carcinoma over a long period of time. Histopathology is still considered to be the most sensitive method in diagnosing breast malignancies in comparison with the other currently available imaging techniques. The morphologic prognostic factors (tumour size, lymph node status and histological grade) have been used as reliable

parameters in assessing the clinical outcome, survival and individualised treatment strategies. These parameters that are assessed by the pathologist represent the basis for categorising the patients in to low risk and high risk groups[55].

COMPARISON OF INCIDENCE OF MALIGNANT BREAST LESIONS:

TABLE 18:

S.no	Name and year of study	Incidence rate
1.	Indian Cancer Society, Mumbai (2001-2003)	27.47%
2.	National Cancer Registry Programme (ICMR) report (2001-03)	25%
3	National Cancer Registry programme, Chennai[31], 2008	28.3%
4	All India Institute of Medical Sciences, New Delhi 2009 -2010	24.3%
5	National institute of pathology, New Delhi[32], 2011	26.3%
6.	Present study	23.12%

As per the reports mentioned in the table 18, current incidence in Chennai is at 28.3%[31]. In our study the prevalence is 23.12%, which is in close correlation with other studies mentioned in the table.

COMPARISON OF AGE INCIDENCE IN PATIENTS WITH BREAST CANCERS:

TABLE 19:

S.no	**Age group**	**Pals et al**	**Reeni malik et al 2003**	**Vissa et al 2011**[61]	**Present study**
1	20-29	10.4	5.36	4.16	2.5%
2	30- 39	26.1	15.66	29.16	16.5%
3	40-49	33	69.95	20.83	35.67%
4	50-59	19.0	69.95	45.83	20.4%
5	60-69	8.0	-	-	16.6%
6	70-79	2.4	-	-	8.3%

While the incidence of breast cancer in western countries is most common in the postmenopausal age group, ie in their 60s and 70s, the incidence is somewhat

different in India with pre-menopausal patients constituting about 50% of all patients.

The age incidence is between 41- 50 years in a study conducted by WHO. In concurrence with the aforementioned studies in table 19, our current study also reveals that the age of peak incidence of malignancy is 40 - 49 years constituting 35.67% of cases. This correlates very well with the study of Pals et al. The mean age in our study is found to be 49.5 years and the age range is found to be 24 – 79 years which is correlating well with the study conducted by khairy et al (age range 24 -81 years)[17] and Emmanuel A et al 2011 (mean age -48.12 years)[11].

CLINICAL PRESENTATION OF BREAST MALIGNANCIES:

Laterality:

TABLE 20:

Side	**Samir S et al**[48]	**Emmanuel A et al 2011**[11]	**Present study**
Left	54.8	50.6	56.1%
Right	45.2	48.9	43.3%
Bilateral	-	0.6	0.6%

In the present study, most of the patients presented with left breast lump (56.1%) as the chief presenting symptom. Table 20 indicates that this finding correlates with the results of Emmanuel A et al 2011[11]. Most of the neoplasms are found in the upper outer quadrant (65 cases). This is in correlation with the findings of kene TS et al and Vincent et al[27] who found that the left breast was frequently involved in their study (62.1%), and the upper outer quadrant was the most commonly affected site (60.7%). Bilateral breast carcinoma constituting a very small proportion of all breast carcinoma cases (l.l-2.4%) is reported in our study in a patient aged 36 years with incidence rate of 0.6% which is a rare occurrence as emphasised by Eleni Tousimis et al[10]. The histopathological type of both the tumours is IDC – NOS type. The right sided tumour measures 4 cm in greatest dimension with TNM stage II and histological grade II and the left sided tumour measuring 1.5 cm is in stage 1 and grade I. Eleni Tousimis et al[10] in his study about the bilateral synchronous breast cancers suggested that they are independently occuring tumours rather than metastasis[15]. Khairy et al[17] in his study found the same histological type in 71.5% of cases of bilateral breast cancer.

Jobsen et al[25] in his study demonstrated that the patients showing bilaterality had a higher distant metastasis (30.8% versus 15.1%, p=0.028) and there is high recurrence rate (29% versus 16%) than those with unilateral lesions. Hence it is emphasised that the bilateral breast carcinomas should be treated aggressively and

advocated regular screening for distant metastasis. Also the patients with unilateral disease should be advised to undergo regular screening of the contralateral breast.

MENOPAUSAL STATUS:

In our study, majority of the patients belonged to premenopausal age group (86 cases, 54.78%). But this finding is more than the observation of Suvarchala SB et al who observed more number of postmenopausal patients (73.4%) in their study group[54].

Nipple discharge:

When the patient presents with nipple discharge, it is considered to be pathologic when it is spontaneous, persistent and contains gross or occult blood. As per the study by Richard J Santen et al[46], among female patients referred to physicians with the presenting symptoms of breast disorder, 6.8% have nipple discharge[46]. But in our study, 25.47% of cases (40 out of 157 cases) presented with nipple discharge.

Vissa et al emphasised that there exists some similarities between the risk factors for the development of Fibrocystic disease (FCD) and those of breast carcinoma[61]. Fibrocystic disease exhibit long term risk for the development of

breast carcinomas and that risk is doubled in patients with complex features including atypical nuclear characteristics, ductal hyperplasias or a family history of breast carcinoma[61]. In our study 3 cases of invasive breast carcinomas are associated with Fibrocystic disease confirming the relative risk of benign proliferative breast diseases for the later development of invasive carcinomas.

SIGNIFICANCE OF PROGNOSTIC AND PREDICTIVE FACTORS IN IDC –NOS TYPE:

It is evident that difficulties prevail in the prediction of the clinical outcome of primary breast carcinoma. Some patients are cured by local therapy, and survive for many years. Some other patients experienced early recurrence of the disease and died shortly after. It would be useful to identify individual patients who have a low or high risk of relapse in order to plan the appropriate management of that patient's breast cancer. Patients with a low risk of recurrence can be spared the potential toxicity associated with aggressive therapy, while patients with tumours that are most likely to recur could be given aggressive adjuvant therapy. Therefore a team work is essential and that should be done by the clinicians and the pathologists in order to select each patient's treatment, according to prognostic and predictive factors.

Hence the diagnostic histopathologist is in an ideal position to convey the clinicians with significant useful prognostic information by the routine examination of mastectomy specimens. In our study with 157 malignant tumours of breast, we have made an attempt to assess the various prognostic parameters which are of clinical importance in order to decide about the individualised treatment strategy.

COMPARITIVE STUDY OF TUMOUR SIZE:

For prognostic correlation the tumour size should be assessed on pathological specimens only, because the clinical measurement is notoriously inaccurate. In our study, the size of the tumour ranges from 1.5 to 15 cm and the mean size is 5.17 cm (S.D. 2.51 cm). This corresponds with the study of Mudduwa et al[28] who found in their study that the tumour size ranged from 0.2 to 14.2 cm, mean size is 3.52 cm wherein the mean size is comparatively more in our study (5.17cm).

TABLE 21:

Tumour size	Gohari MR[16], et al, (2006)		Onitilo et al[35], 2009		Present study	
	No of cases (n=117)	%	No of cases (n=1134)	%	No of cases (n=157)	%
< 2 T1	21	18.6	810	71.4	26	16.56
2-5 T2	57	50.4	262	23.1	56	35.67
>5 T3	27	23.9	53	4.7	68	43.31
Skin or chest wall T4	8	7.1	-	-	7	4.46

In our study, majority of the cases (72/154) have the tumour size >5 cm in maximum dimension constituting 43.31%. Table 21 indicates that this finding is comparatively more than the western literature by Onitilo et al[35] where majority of cases falls within the tumour size < 2 cm in 810/1134 cases (71.4%).

This indicates that majority of cases in our study presents in the late stage as size of the tumour is a time dependant variable in contrast with the western countries where the breast tumours are diagnosed in the early stage <2cm because of adequate screening programs and awareness.

COMPARITIVE STUDY OF AXILLARY NODAL STATUS:

TABLE 22:

S.no	Name of the study	No of cases	Lymph node status		
			I (node negative)	II(1-3 positive)	III(>4 positive)
1	ONITILO et al[35]	1134	61.2	35	-
2	Uribe et al[59]	7,798	67	33	
3	Christopher et al[8]	5750	57.8	17.1	8.7
4	Bharat et al 2005[52]	569	19.8	80.2	
	Present study	154	16.89	48.05	35.1

Table 22 indicates in the present study, patients with positive 1-3 nodes and more than 4 positive lymph nodes constitutes 48.05% and 35.1% respectively correlating with the Indian report of Bharat et al 2005[52]. The most important benefit of axillary lymph node dissection (ALND) is the prognostic information it gives in deciding about systemic therapy. Patients with four or more involved nodes at initial diagnosis have a significantly worse outcome than node-negative

cases, regardless of the duration of the disease-free interval. Positive axillary nodal status is considered as a marker of an aggressive phenotype[23].

DISTANT METASTASIS

In the present study none of the patients presented with distant metastasis. But in the study conducted by Agarwal et al,[39] it is documented that 6-25% of individuals with breast cancer in India have metastasis to distant organs at the time of presentation.

COMPARITIVE STUDY OF TNM STAGING:

TABLE 23:

S.no	Name of the study	No of cases	Stage(%)		
			I	II	III
1	Onitilo et al 2009[35]	1134	56.4	36	7.7
2	DJ Uribe et al[59]	7,798	53	38	9
3	Christopher et al[8]	5750	51.6	37.7	6.3
4	Agarwal et al[15],lucknow 2007	544	4	34	51
5	Vinod et al[60], New Delhi2005	487	16	74	-
6	Present study	154	16.8	36.37	46.75

Table 23 shows that Pathological staging of breast carcinomas in our study showing 16.8% of the tumours presenting in stage I disease which is in correlation with the study of Vinod et al[60]. 36.37% are seen in stage II, 46.75% in advanced stage III, correlating with the study by Agarwal et al[15] which are previous Indian reports.

But the studies done in developed countries have shown that more percentage of cases are seen in stage I disease which implies that the breast carcinomas are detected in an early stage in the developed countries.

INCIDENCE OF HISTOLOGICAL TYPES:

In our study Invasive ductal carcinoma NOS type observed in 144 cases stands as the most common carcinoma of the breast (91.71%). In that 6 cases are associated with Paget's disease.

Few rare neoplasms like Invasive lobular carcinoma, Cribriform carcinoma, Medullary carcinoma, Mucinous carcinoma, Invasive papillary carcinoma, Micropapillary carcinoma and Metaplastic carcinoma are also observed in our study.

TABLE 24:

S.no	Histological types	Ivar et al[24] 2010	Emmanuel et al[11] 2011	Mauro et al[30]	Current study
1	IDC – NOS type	81.4	87	80.63	87.89%
2	IDC with Paget disease	1.5	-	1.05	3.82%
3	Invasive Lobular carcinoma	6.3	3.6	1.05	0.64%
4	Cribriform carcinoma	-	-	1.05	0.64%
5	Mucinous carcinoma	1.5	1.8	2.62	2.54%
6	Medullary carcinoma	1.1	1.2	0.52	0.64%
7	Papillary carcinoma	1.2	0.6	2.09	0.64%
8	Micropapillary carcinoma	1.2	-	0.52	0.64%
9	Metaplastic carcinoma	1.2	-	1.05	0.64%

10	Malignant Phylloides tumour	-	1.8	0.52	1.91%

Table 24 shows that the Incidence of histological types in our study correlates well with the study of Emmanuel et al 2011[11] and Mauro et al[30]. Other rare special types which constitute <1% also correlate with other studies.

COMPARITIVE STUDY OF CASES IN EACH GRADE WITH OTHER STUDIES:

Histological grading is one of the validated prognostic variable and its exclusion from clinical decision making may result in overuse of adjuvant therapies in breast cancer. The most widely incorporated system of Elston - Ellis system which represents a modification of SBR system is used in our study.

TABLE 25:

S.no	Name of the Study	No of cases	Grade		
			I	II	III
1	Frkovic-grazio and bracko et al., 2002[40]	270	38	38	24
2	Warwick et al., 2004[62]	1988	23	37	40

3	Williams et al., 2006[65]	1058	20	46	34
4	Rakha et al., 2008[40]	2219	18	36	46
5	Thomas et al., 2009[57]	1650	26	45	29
6	Blamey et al., 2009[13]	16,944	29	41	30
7	Present study	145	17.9	49.7	32.4

Table 25 shows that in our study, most of the breast cancers are in the grade II which correlated with the study of Williams et al., 2006[65]. But in comparison with most of the western literature where more cases are picked up when they are as grade I lesions, our study shows 32.4% of cases in grade III. As per the previous reports, high grade lesions have early recurrence and metastasis and so there is justification for prompt use of chemotherapy and low grade lesions can be subjected to long term follow up with or without systemic therapy. Thus assessment of histological grade when carried out adequately is an important determinant of breast cancer prognostication and should be evaluated to define the individualised treatment.

Thus, applying the algorithm of clinical determinants like TNM staging which takes in to account the tumour size, nodal status and distant metastasis and histopathological types and grading in our study, it could be possible to identify

individual group of patients whose prognosis is so good or so poor. It is also possible to comment whether the aggressive adjuvant therapy is warranted by the histopathological parameters and the results are correlating with the previous Indian studies and reports.

CORRELATION OF AGE WITH OTHER PROGNOSTIC VARIABLES:

As age is also a prognostic factor mentioned in the literature, we have made an attempt to correlate the age of the patient and the TNM classification at clinical presentation.

Out of the 4 cases in 20-29 age group in our study, 2 cases had tumour size more than 5cm. Maximum percentage of 19.11% (>5cm) is seen in 40-49 year age group compared to older age group.

These observations are correlating with the study of Schnitt et al and Pascal et al who ascertained through their observations that the tumours in young patients are more commonly seen with increased tumour size[33,36].

In our study, younger patients frequently have >4 positive lymph nodes with 20 out of 54 (12.99%) in 40-49 year age group wherein it is 4 out of 54 (2.6%) in 70-79 age group. This correlates with the observation by Paul et al[14] who observed that 37% of patients who were less than 40 years in contrast with only 25% of patients > 40 years presented with lymph node metastasis.

We found that the mean age was high in patients with stage I disease (49.5 years) when compared with the mean age of women with stage III disease. In our study out of the four patients in 20-29 age group, 3 cases were found to be in stage III. This observation is similar to that of Foo CS, et al., (2005)[12] who has come with the observation that the younger patients have tumors with advanced stage and poorer prognostic parameters. Hanna et al, 2009 emphasises that overall survival is poor in younger patients[20] (74.7% in 20 – 34 years vs 87.8% in 50 – 69 years) despite the aggressive adjuvant therapy to which they are subjected. The factors that are thought to be responsible for worse prognosis in young women are late presentation and more aggressive tumour biology.

Age and histological grade:

Our study results show out of the 4 patients in 20 - 29 year age group, 2 cases each is seen with grade II and grade III tumours respectively. Most of the patients (17 out of 46) in grade III are in the 40-49 age group (11.81%).

This inference is in parallel with the study of Schnitt et al and Pascal et al who observed that younger age group patients usually have breast carcinomas with grade 3 histological features[33,36] and greater tumour size.

CORRELATIVE STUDY OF HISTOLOGICAL GRADING WITH OTHER PROGNOSTIC VARIABLES:

Cases of invasive ductal carcinoma were alone included in this correlation. We had 144 cases in this category.

Size and grade:

In analysing the cases of breast carcinoma, we attempted a correlation between the histological grade of malignancy and the mean tumour diameter. We found in grade I lesion the mean tumour size was 1.98 cm, for grade II lesions it was 5 cm and grade III lesions had a mean tumour size of 6.93 cm**.** These results were statistically significant with a P value of 0.0001 (Table 12) This correlates well with the results of Sundquist M, et al.,[29] who has shown that the accurate estimation of the tumour size together with the grade and lymph nodal status are documented statistically significant predictors of survival .

Lymph Node Status and Grade:

Axillary node involvement is an important prognostic parameters in the management of breast cancer.

Rack and Gerber et al., found that primary lymph node involvement is not only a time-dependent indicator for tumour extension, but also indicates tumours with aggressive biological behaviour. On correlation of lymph node stage with the histological grade of the tumour, it is found that among grade II, maximum number of cases (55 out of 72) with 83.33% have positive 1-3 lymph nodes. Most of the

grade III cases (35 out of 46 cases with 76.09%) have > 4 positive lymph nodes. This is similar to the finding of Hung et al who documented that higher histologic grade was associated with more positive lymph node metastasis (P 0.001)[51].

TNM stage and Histological grade:

There is an excellent correlation between the TNM staging and histological grading. As out of the 56 cases presenting as stage II disease, 46 cases fall into the grade II category and out of the 72 cases presenting as stage III diseases, 43 cases (62.32%) belong to grade III followed by 26 cases of grade II malignancy. This finding is similar to that of Rosen PP, et al., who found significant poorly differentiated features in malignancies with advancing stage. Hensen and freedman et al found that the 5-year relative survival rate for Stage I, Grade 1 tumours was 99% and it is reduced for Stage I but Grade 2[21] tumours. In stages II-IV, histologic grade has important prognostic role. Thus assessing histological grade with staging improves the prediction of outcome.

HORMONE RECEPTOR STATUS IN BREAST CARCINOMAS:

As Breast cancer is hormone dependant and the tumour cell population that expresses ER positivity depend on estrogen to grow. Hence, anti-estrogen hormonal therapy blocks the receptors so that the cancer cells may undergo death. Onitilo et al.,[35] 2009 documented that ER+,PR+ tumours have a lower incidence of

recurrence and a longer disease-free interval, regardless of tumour size or lymph node status[54]. Thus, hormone receptor positive tumours tend to have a significantly longer disease free survival than the receptor negative tumours[7,26,43]. Therefore, in our study we attempted to know the hormone receptor status in selected 20 cases of invasive epithelial malignant tumours.

In a study conducted by Rhodes et al., 2000 in 7016 breast carcinomas, it was found that estrogen, progesterone receptors were positive in 54.8%, negative for both receptors in 22.1% of cases[43].

Col.V. Dutta et al (2008) conducted a study in 75 breast cancers in Armed Forces Medical College, Pune and on evaluation found that 33% of (25/75) cases expressed ER, PR or both whereas 67% (50/75) were found to be negative for both the receptors. This study reveals that negativity for receptor status is higher in our Indian subset of tumours compared with western population.

Tanuja Shet et al.,[56] (2009) studied hormone receptor expression in the last 8 years from 1999 to 2006 in a cancer referral centre in India. A total of 11,780 cases were reviewed. The percentage of hormone receptor expression varied from 52% to 57%.

In the present study among the twenty cases in which hormonal receptor study has been done, only estrogen receptor positivity is seen in 65% of cases and

both receptors were negative in 35% cases (Table 15 & 16). Hence this study is comparable with the studies conducted in the Indian subset of tumours. There appears to be a minimal variation in receptor expression; this could be explained by differences in the technique of evaluation and inter-laboratory quality control variations.

CORRELATION OF ER, PR STATUS WITH AGE AND MENOPAUSE:

In the present study, on correlating the hormone receptor status with the age group, it was found that the positivity increases in older age group (50-59 years) which is correlating with the results of Suvarchala SB et al[54] whose observation is that the receptor positivity status increases with age and also with many previous reports.

Kaiser Jamil et al[26] compiled with his observations that the individualised therapy can be offered to the patients by studying the ER, PR status on the basis of menopausal status. The overall percentage of the receptor status shows that Estrogen positive and progesterone negative tumours (ER+ and PR-) are more common in postmenopausal patients in the present study group (50%). The hormone negativity is more common in the premenopausal group of patients (50%).

This is in correlation with the most previous studies which emphasised the menopausal status suggesting that the degree of receptor positivity is lower in premenopausal women than the postmenopausal age group (Kenneth et al). The present study is also very well correlating with the study by Kaiser Jamil et al[26] who found greater number of ER+PR- cases in the postmenopausal age group (29.11%).

Kaiser Jamil et al[26] in his study also correlated the receptor status in breast cancer patients with therapy regimens like chemotherapy, hormone therapy with various medications. Postmenopausal women with ER+/PR- and ER-/PR- tumours who have been treated with the combination of these medications manifested better outcome in the form of tumour regression and decreased mortality than the premenopausal women.

ER, PR status in different histological types:

In different special types of breast cancers, it was found that 25% (5 of total 20 cases) of IDC - NOS type were positive for both ER and PR. This is low when correlating with the previous literature which reported 70-85% positivity in IDC-NOS type. This can be accounted by the fact that hormone receptor positivity varies according to the race, ethnicity, differentiation and aggressiveness of the tumour. In correlation with the literature by Suvarchala SB et al,[54] the Lobular

carcinoma is ER positive and has focal PR positivity whereas the Mucinous variant is ER+ but PR-. This can be accounted by the difference in standardisation procedures and fixation processes affecting the results. In correlation with the literature by Uribe et al[59], the Medullary and Metaplastic carcinomas are negative for ER and PR and the Papillary carcinoma is positive for both.

SUMMARY

In the two year study period from June 2010 – July 2012 in the Department of pathology, Madurai medical college, the breast lesions accounted for 679 cases. Out of this, this prospective study by assessing 157 cases of malignant tumours of breast treated by mastectomy with the clinical parameters, light microscopic findings and study of hormone receptors by Immunohistochemistry, the following conclusions are made and presented.

1. The incidence of malignant breast tumours is 23.12%.

2. Malignant neoplasms commonly occur between 40-49 years accounting for 35.7%. All the 157 mastectomies included in the study are female patients only. Left sided breast lump is the commonest presentation (88/157 cases) and the Upper, outer quadrant is the usual site for the breast lumps (75/157 Cases).

3. Out of the 157 cases, 86(54.78%) cases are in premenopausal age group and 71 cases (45.22%) are in postmenopausal age group. Malignant tumours in our study are common in premenopausal age group.

4. Out of 157 cases, 144 Invasive Ductal Carcinoma (NOS) are encountered in this study and it is the commonest malignant Neoplasm constituting 91.71%. Out of this, 6 cases (3.82%) are associated with Paget's disease. 4 cases are Mucinous carcinoma constituting 2.54%. Other special types such as Lobular, Cribriform, Papillary, Micropapillary, Medullary and Metaplastic Carcinoma (one case in each type) constitute 3.54%. 3 cases are Malignant phylliodes tumour constituting 1.91%.

5. Tumours with size <2 cm are seen in 26 cases (16.56%), 2-5 cm seen in 56 cases (35.67%), more than 5 cm seen in 68 cases (43.31%). 7 patients (4.46%) presents with tumours extending up to skin. Most of the breast malignancies in our study have > 5 cm tumour size.

6. Node negative cases are 26 (16.89%), 74 cases (48.05%) presents with 1-3 lymph nodes with metastatic deposits and 54 cases (35.1%) presents with >4 positive lymph nodes. Majority of cases show 1-3 positive lymph nodes.

7. 26 cases (16.88%) are in TNM stage I, 56 cases (36.37%) in TNM stage II and 72 cases in TNM stage III (46.75%). Maximum number of cases are seen in TNM stage III.

8. Grading is a very beneficial protocol in assessment of prognosis and management. 26/144 cases of IDC-NOS type are seen as grade I lesions (18.05%), 72/144 cases as grade II lesions (50%) and 46/144 cases (31.95%) as grade III lesions. Most of the epithelial malignancies are seen as grade II lesions.

9. The breast carcinomas in young women have mean tumour size 7.75 cm, most of them with TNM stage III disease at presentation and of higher histological grade.

10. Histological grade as prognostic tool correlates well with other prognostic variables like tumour size, axillary nodal status and TNM stage.

11. In the hormone receptor study done in 20 selective cases of IDC-NOS type (10 cases in premenopausal age group and 10 cases in postmenopausal age group), estrogen receptor positivity is seen in 65% of cases, negativity for both ER and PR receptors in 35% of cases with increase in positivity in older age group (50-59 years).

12. ER+, PR- tumours (5/10 cases) are more prevalent in postmenopausal age group constituting 50%.

13. Special histological variants like Papillary Carcinoma, Lobular Carcinoma are positive for ER and PR. Medullary and Metaplastic variants are negative for both receptors. Mucinous variant is positive for ER and negative for PR.

CONCLUSION

The present prospective study of clinicopathological correlation of breast carcinomas highlights the importance of evaluation of clinical parameters and their correlation with the prognostic significance of histopathological parameters. In this analysis, it is found that the number of patients presented with advanced stage and grade is more in younger age group than older age group.

So we conclude that an appropriate clinical evaluation of patients along with the assessment of basic histopathological prognostic parameters and Immunohistochemical study of hormone receptor in breast cancer patients will lead on to a precise and individualised management which will have better impact on the disease free survival and overall survival.

Although different treatment modalities are available, Prevention is always better than cure. So the obstacle for affording the health facilities that commonly prevails among women in our country should be sought by creating awareness and implementing regular mammographic screening among all the women, with specific importance to, young women at risk for developing the breast cancer. With better awareness and screening the incidence and mortality rate of breast cancer can be reduced for which a coordinated effort is essential.

FIG 1: Invasive ductal carcinoma with irregular border. (569/12)

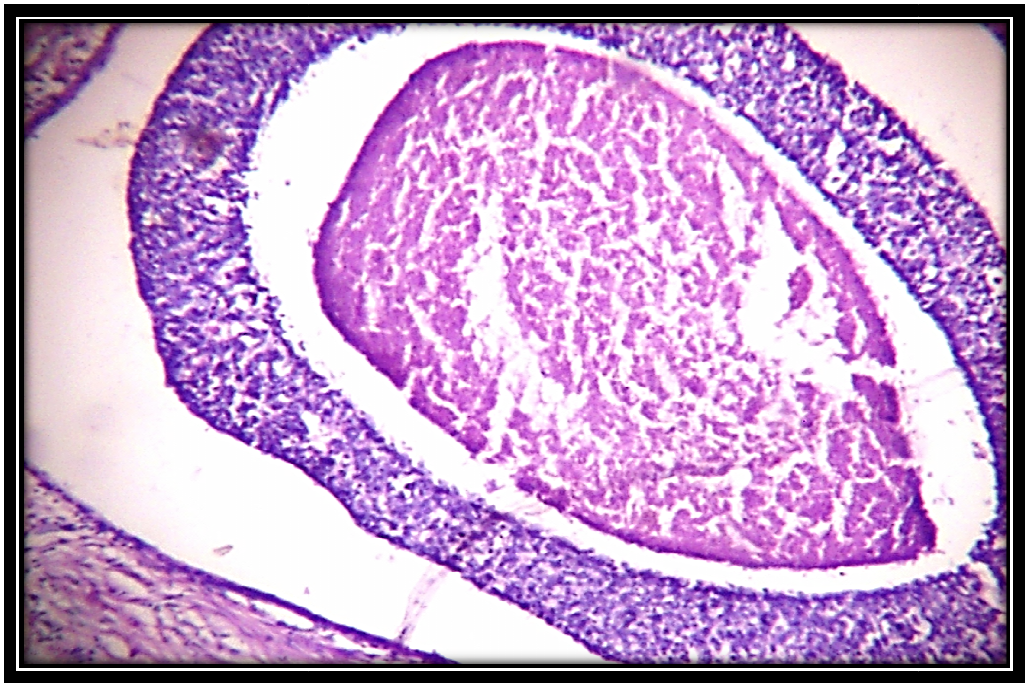


FIG2: Invasive ductal carcinoma with comedo pattern of necrosis. H & E x100 (1664/11).

FIG 3: Mucinous Carcinoma of breast with Gelatinous appearance. (2273/12).

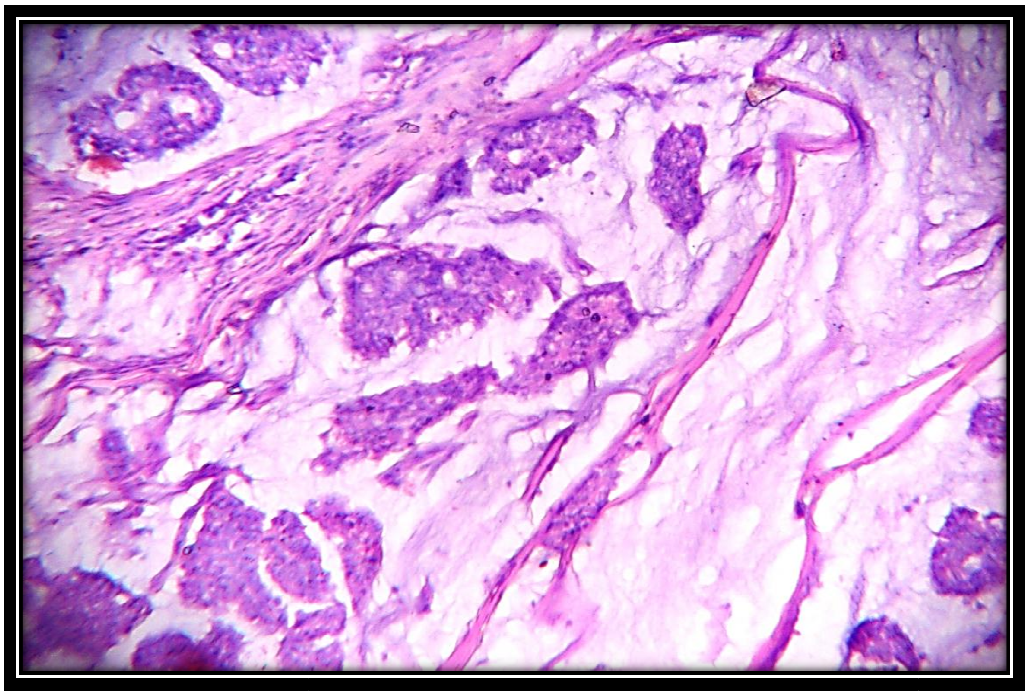


FIG 4: Mucinous carcinoma of breast showing malignant cells within pools of extracellular mucin. H & E x100(2273/12).

FIG 5: Paget's disease of nipple showing erythematous eruption with scale crust. (1520/12).

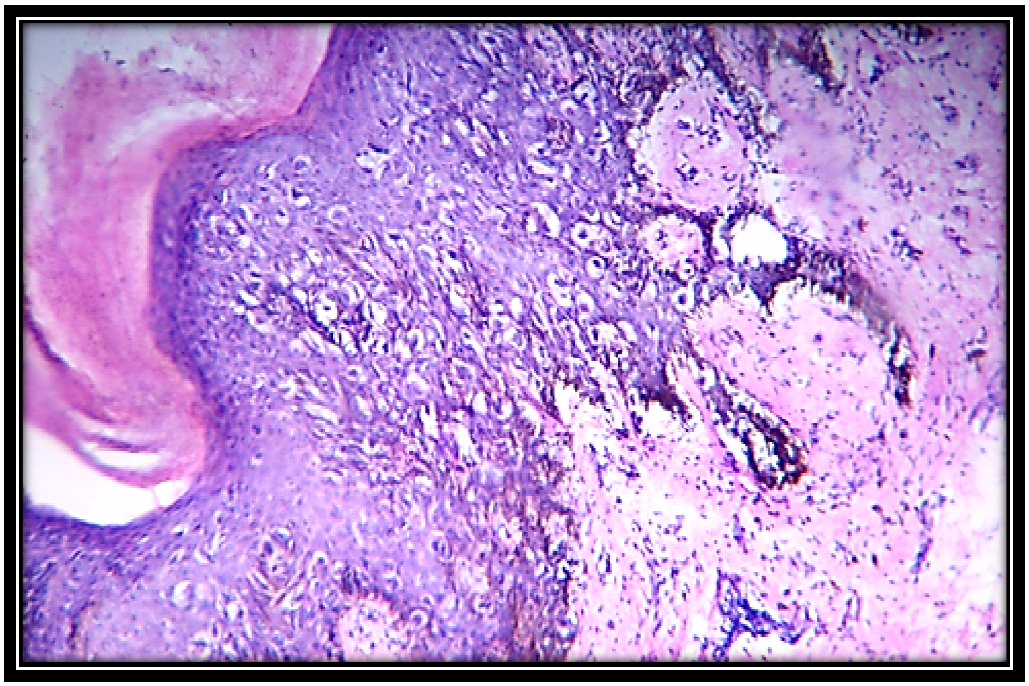


FIG 6: Paget's Diseaseof the nipple showing Atypical cells with clear cytoplasm (Toker cells). H & E x100 (1520/12).

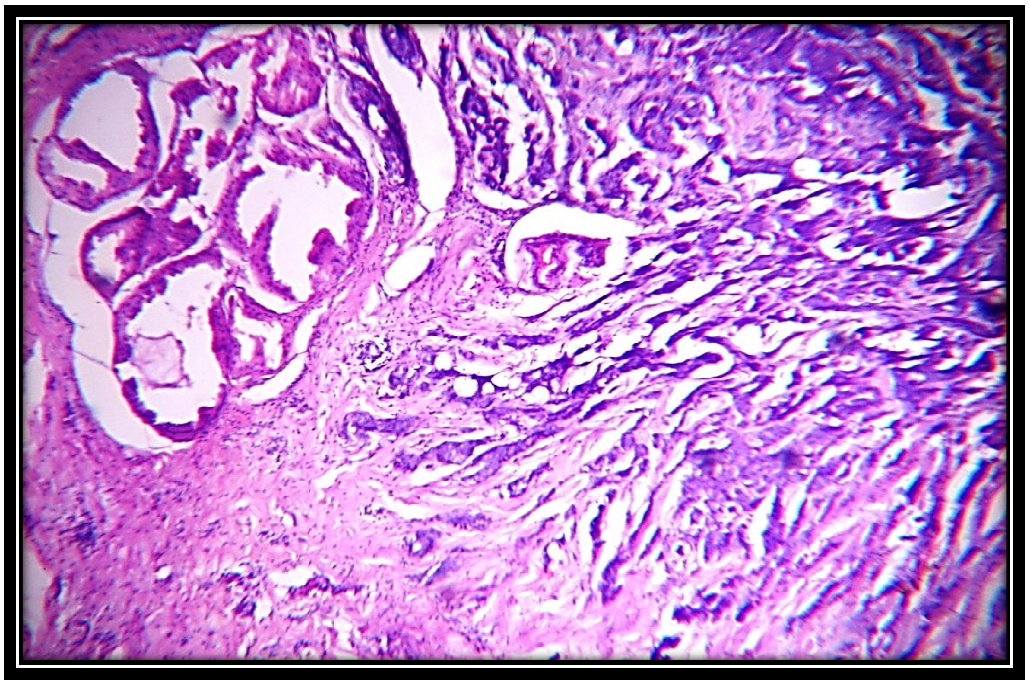


FIG 7: Invasive ductal carcinoma associated with Fibrocystic disease. H & E x100 (3329/11).

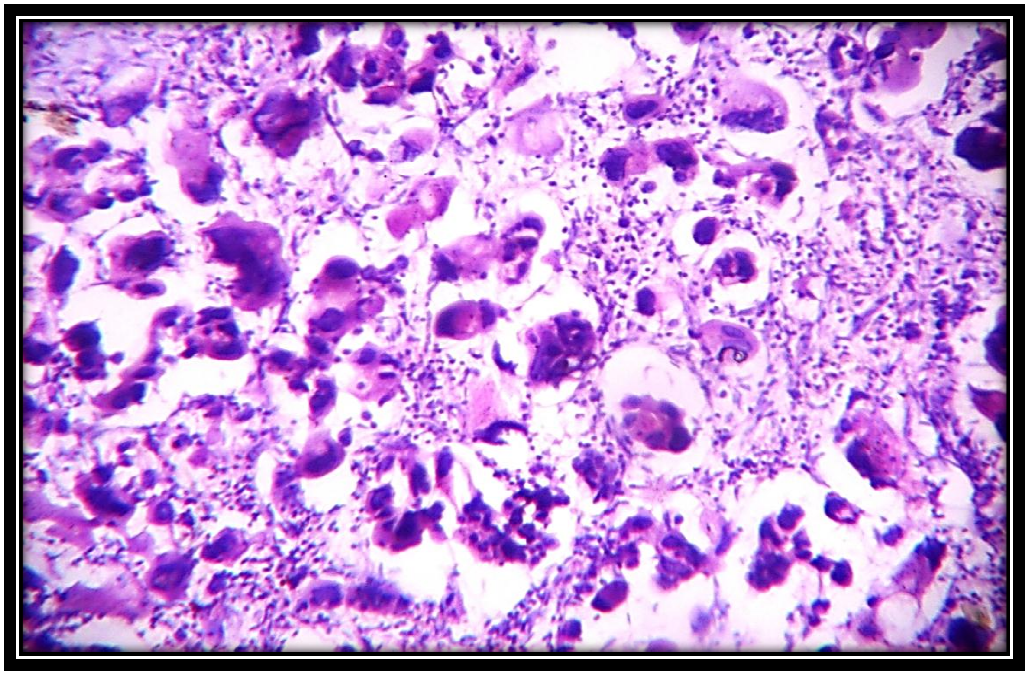


FIG 8: Invasive ductal carcinoma with multinucleated giant cells in the stroma. H & E x100 (2069/12).

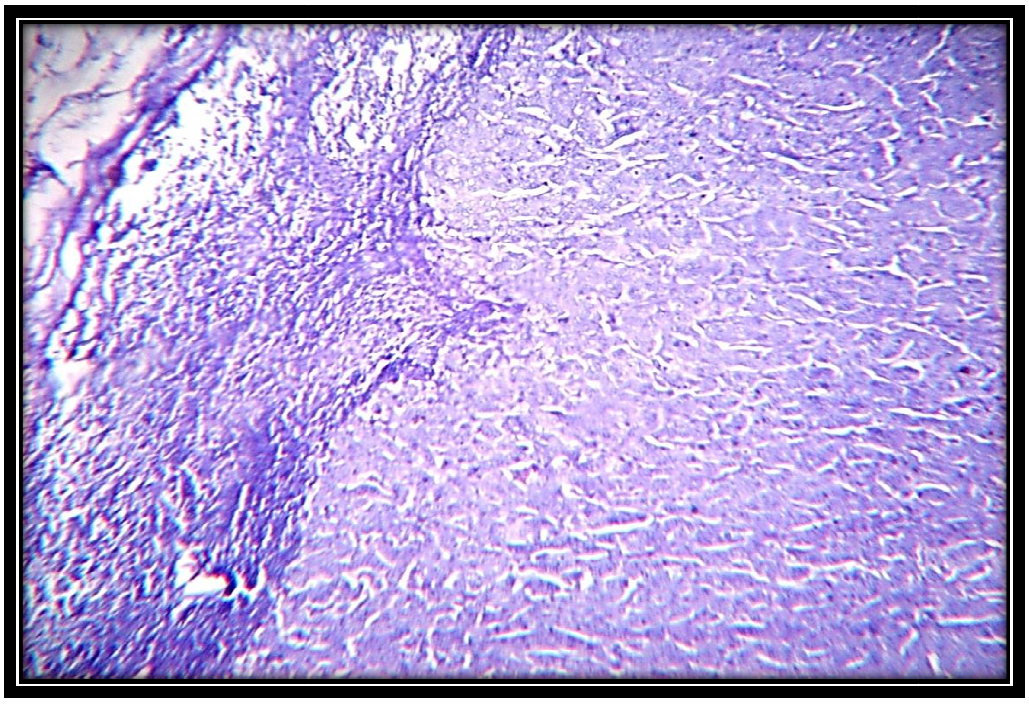


FIG 9: Metastatic deposits of Invasive ductal carcinoma in lymph node. H & E x100 (2293/12).

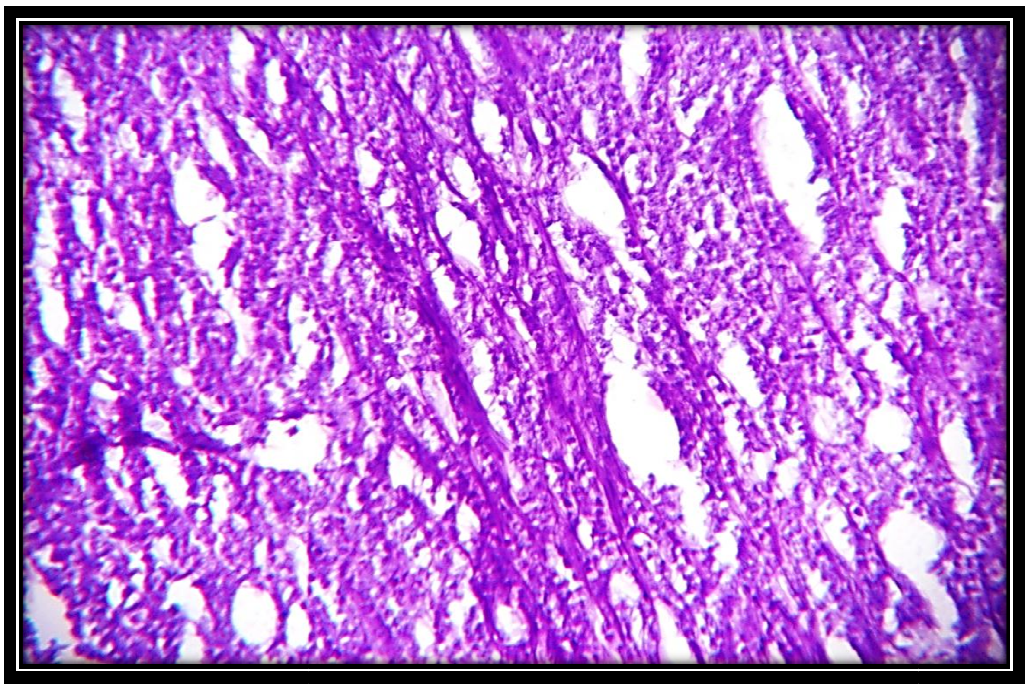


FIG 10: Invasive Lobular carcinoma showing Indian file like pattern of growth. H & E x100(4130/11).

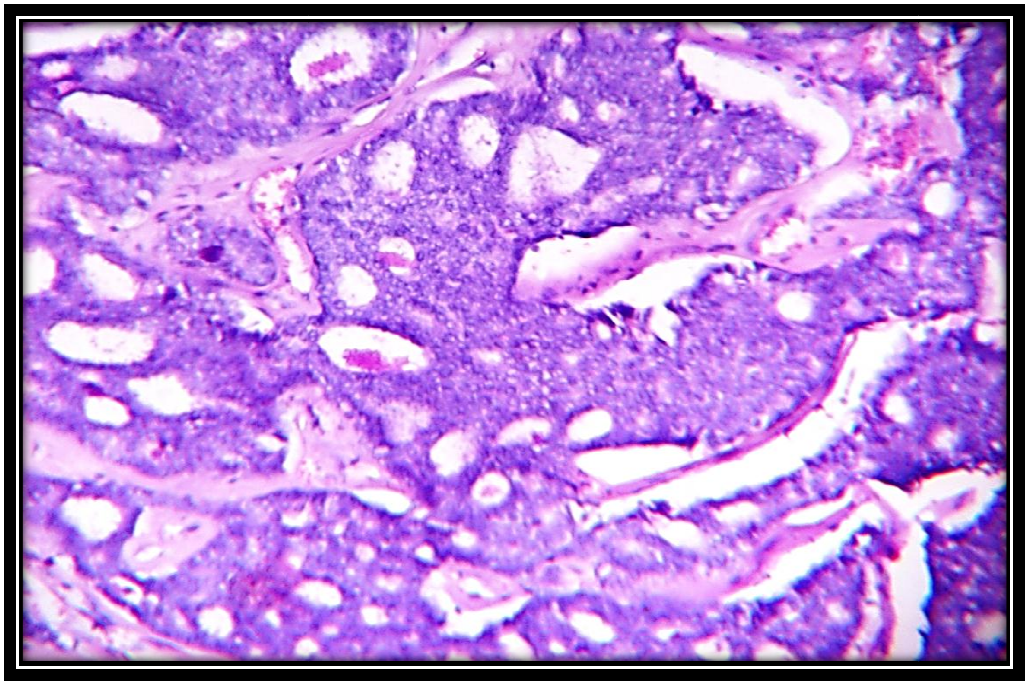


FIG 11: Invasive Cribriform carcinoma showing tumour cells arranged in cribriform pattern. H & E x100 (925/12).

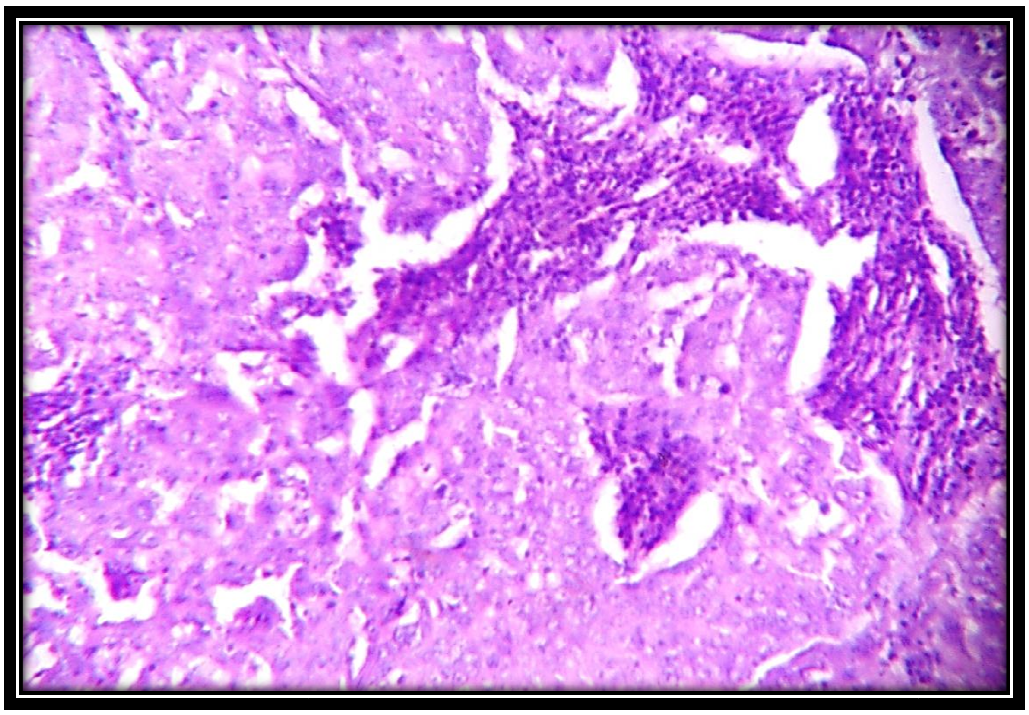


FIG 12: Medullary carcinoma composed of syncytial sheet of large pleomorphic cells. The adjacent stroma contains numerous mature lymphocytes. H & E x100 (1125/12).

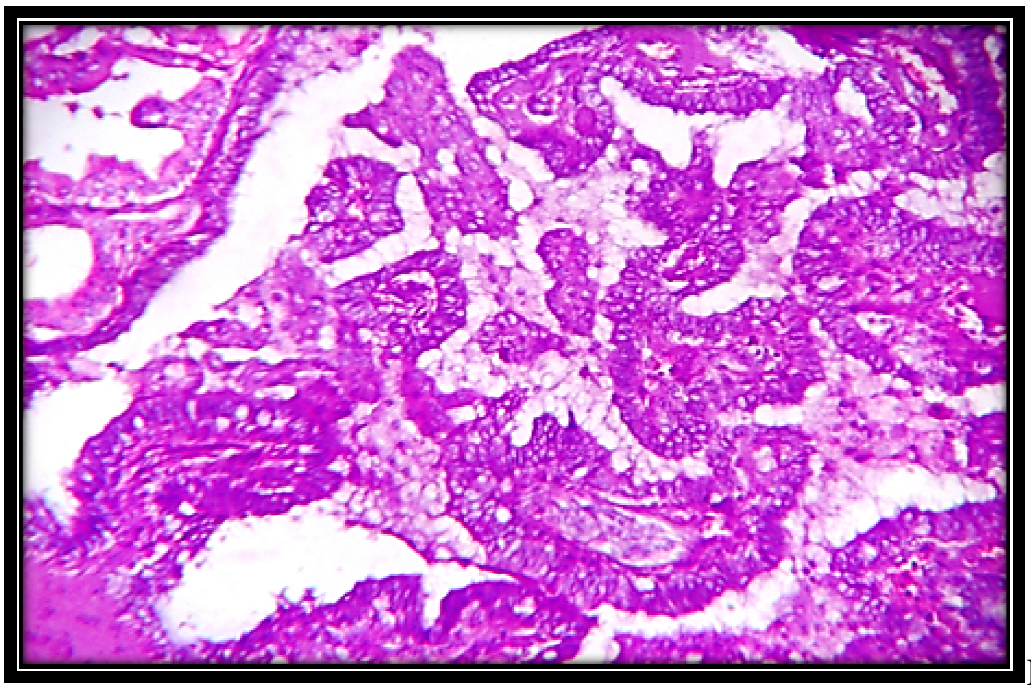


FIG 13: Papillary carcinoma of breast showing delicate and blunt papillary formations. H & E x100 (2893/10).

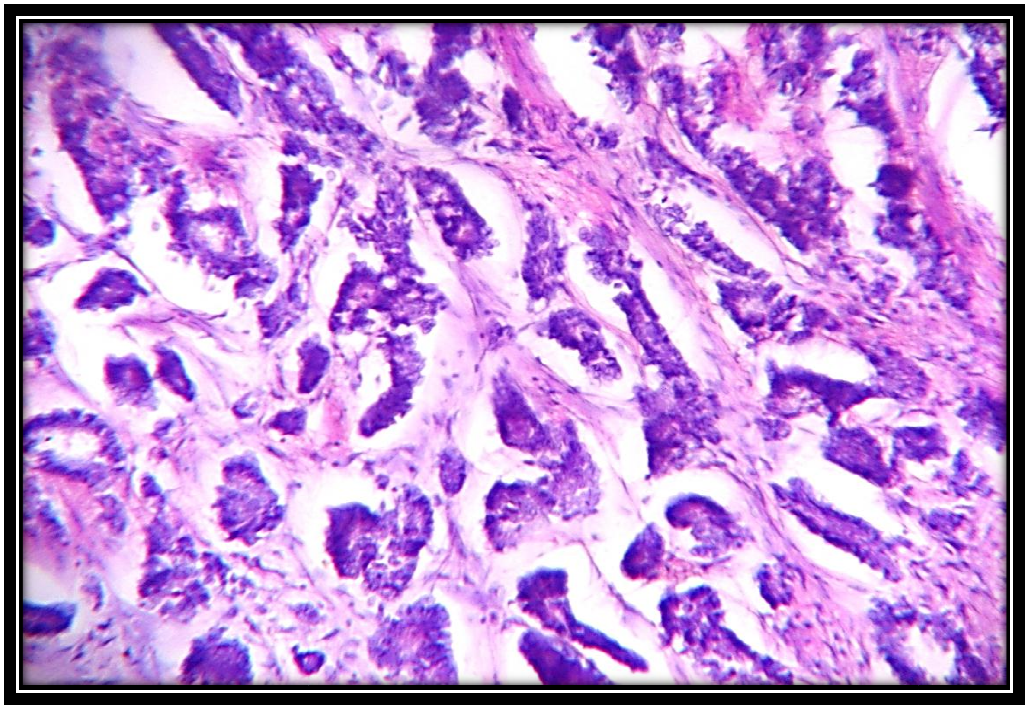


FIG 14: Invasive Micropapillary carcinoma showing Tumour cell clusters within empty stromal spaces. H & E x100 (2156/12).

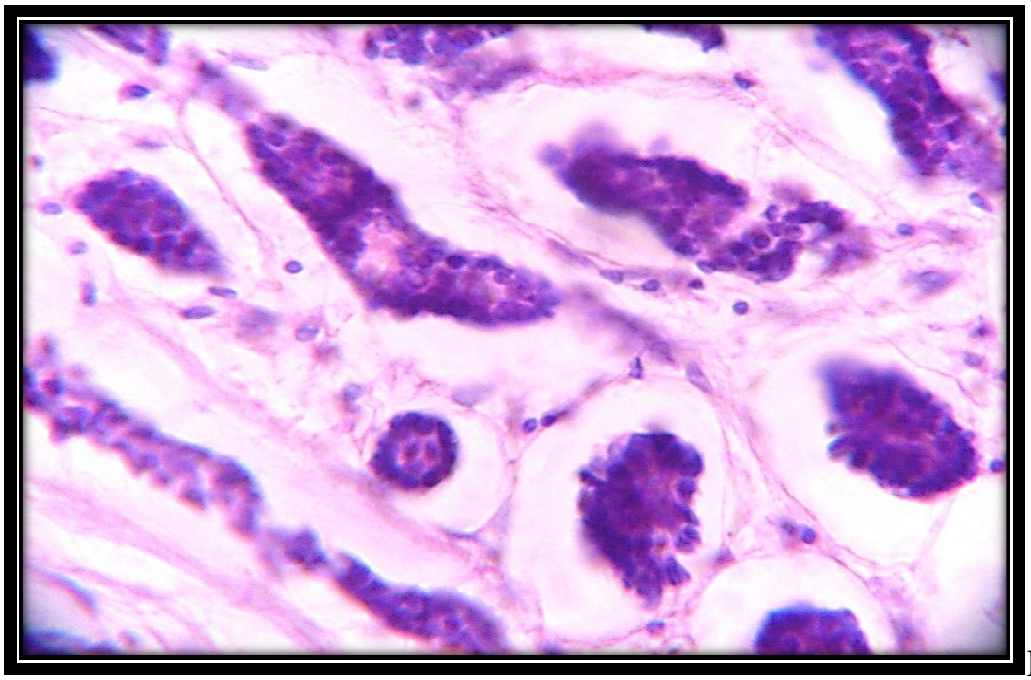


FIG 15: Invasive Micropapillary carcinoma. Tumour cells have reversed polarity with an "inside out" morphology. H &E x400 (2156/12).

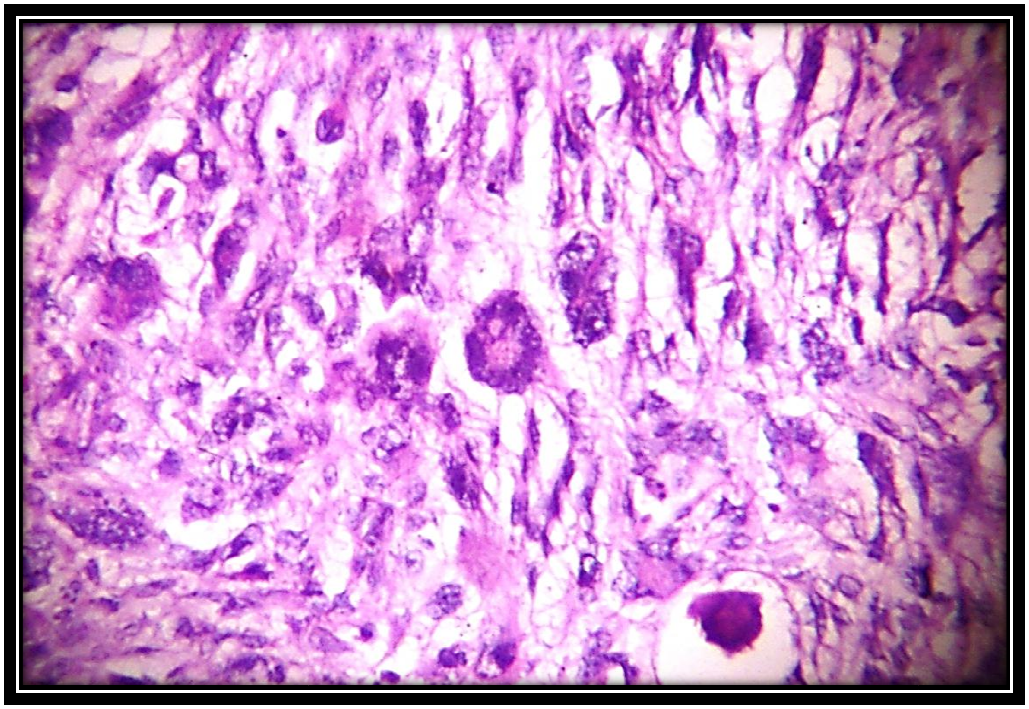


FIG 16: Metaplastic carcinoma exhibiting biphasic (carcinosarcomatous) appearance. H &E x100 (3305/11).

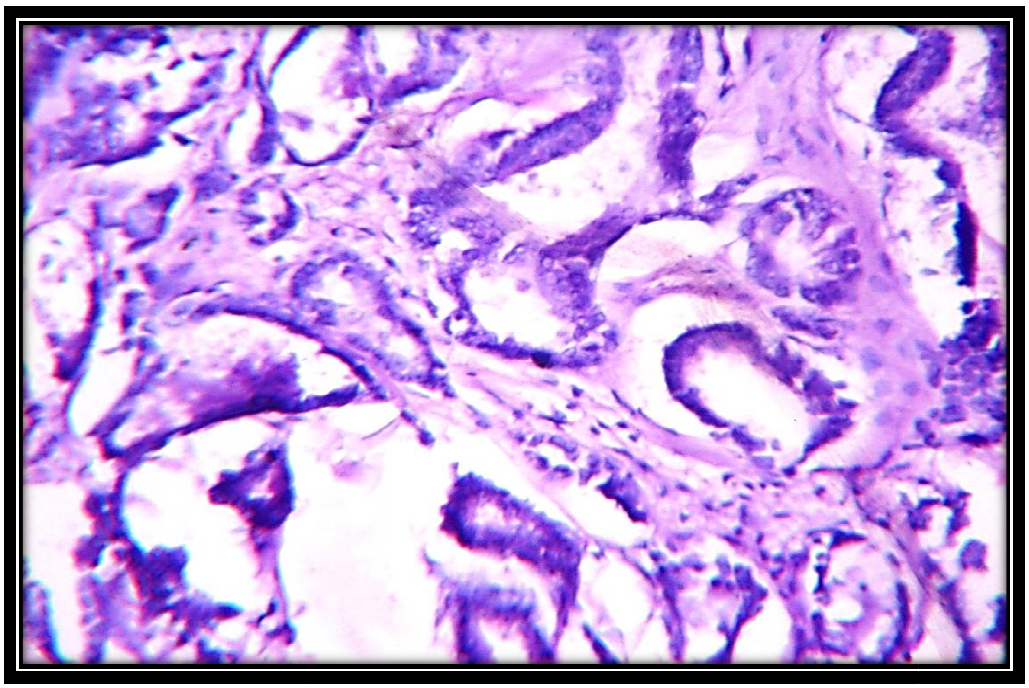


FIG 17: Invasive ductal carcinoma - Histological Grade I showing tubules. H &E x100 (2120/10).

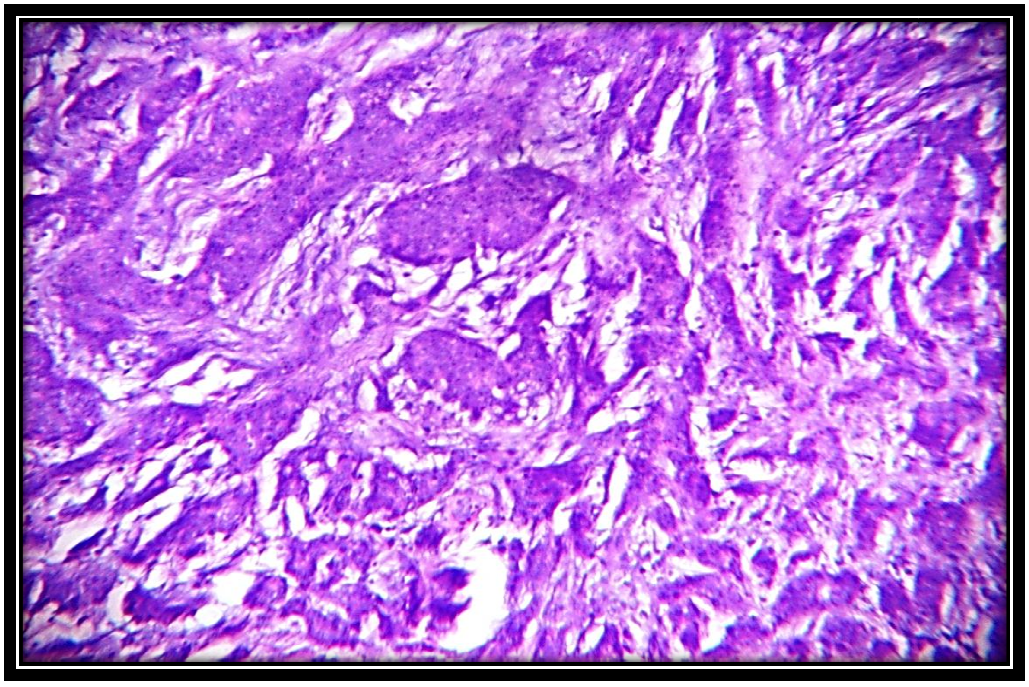


FIG 18: Invasive ductal carcinoma-Grade II. H &E x100 (1686/11).

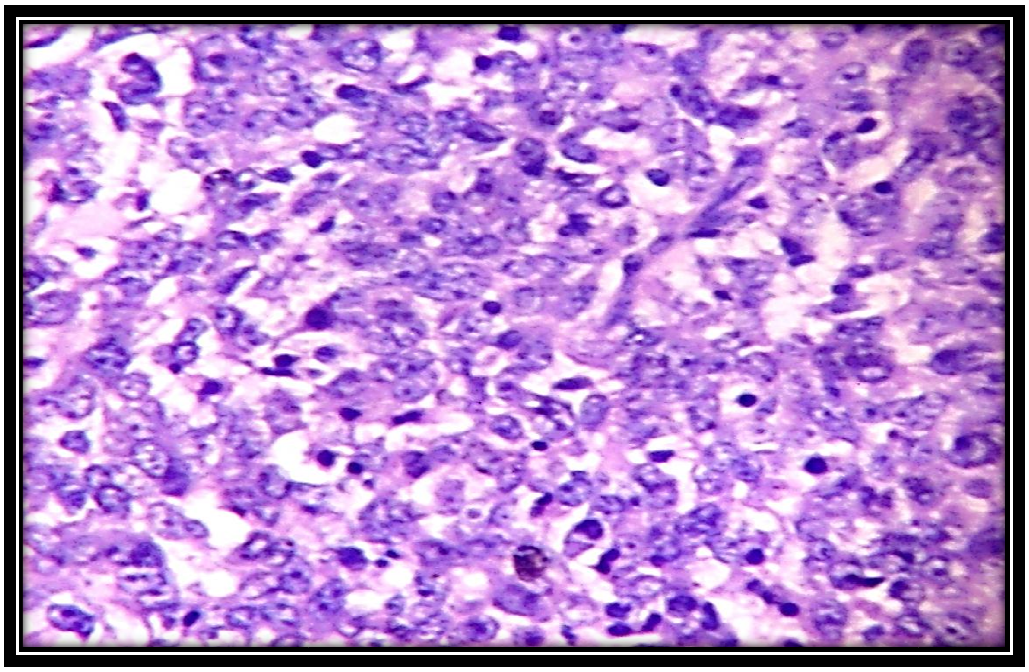


FIG 19: Invasive ductal carcinoma Grade III with no evidence of glandular differentiation. H &E x400 (872/12).

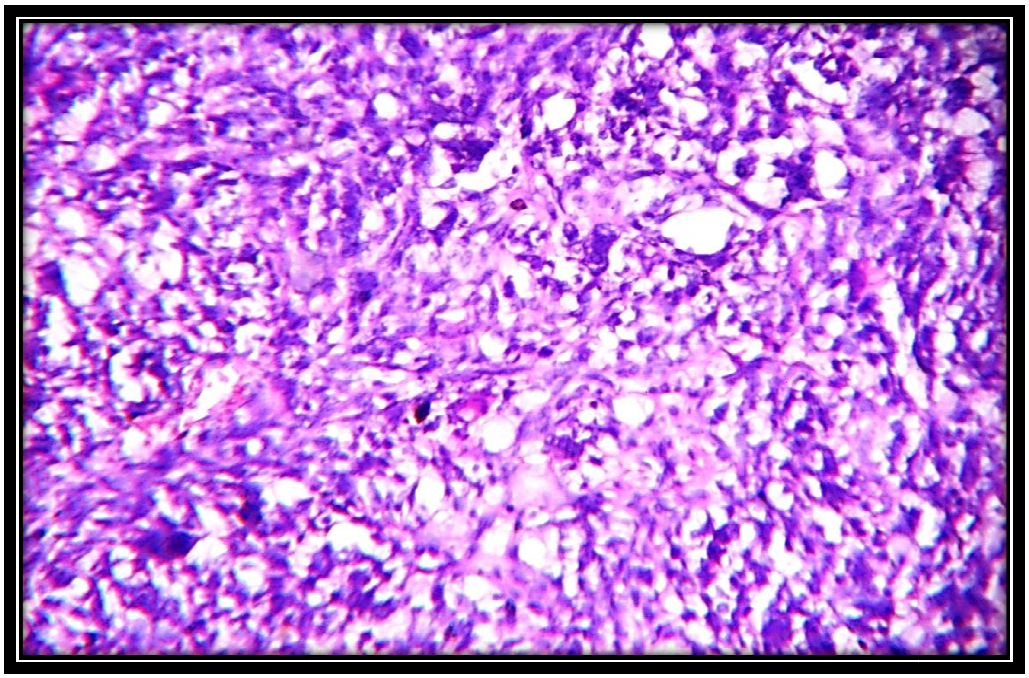


FIG 20: Malignant phylloides tumour of breast showing severe stromal atypia and multiple mitoses. H & E x100 (3622/11).

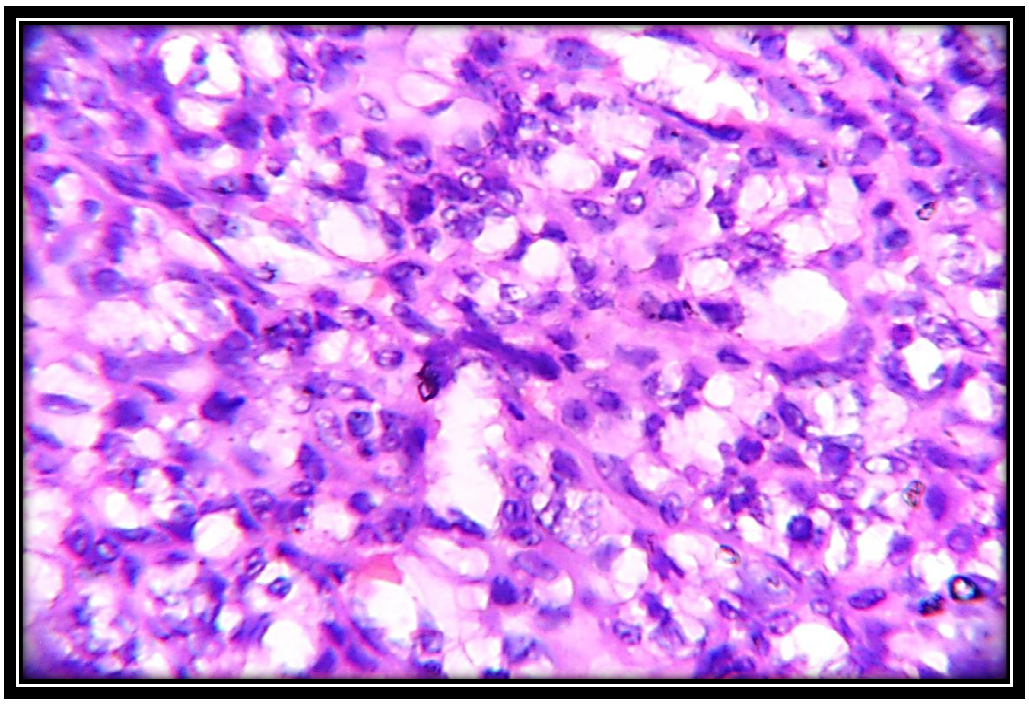


FIG 21: Malignant phylloides tumour of breast showing numerous mitotic figures. H & E x400 (3622/11).

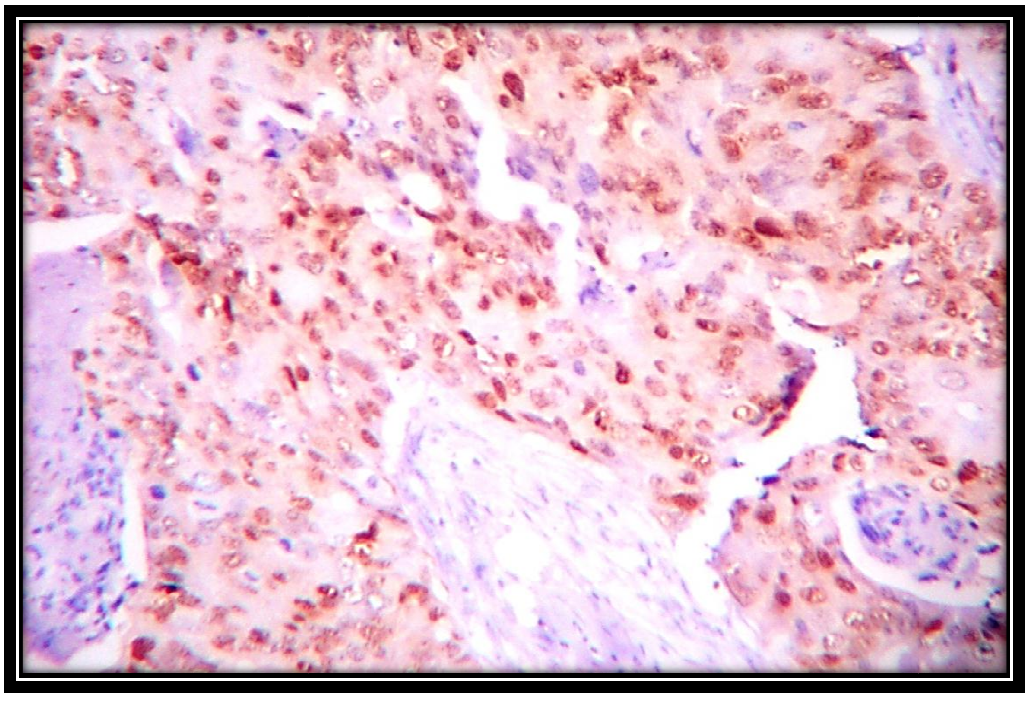


FIG 22: Immunohistochemistry for Estrogen receptors showing strong nuclear positivity in tumour cells. x100 (1574/12).

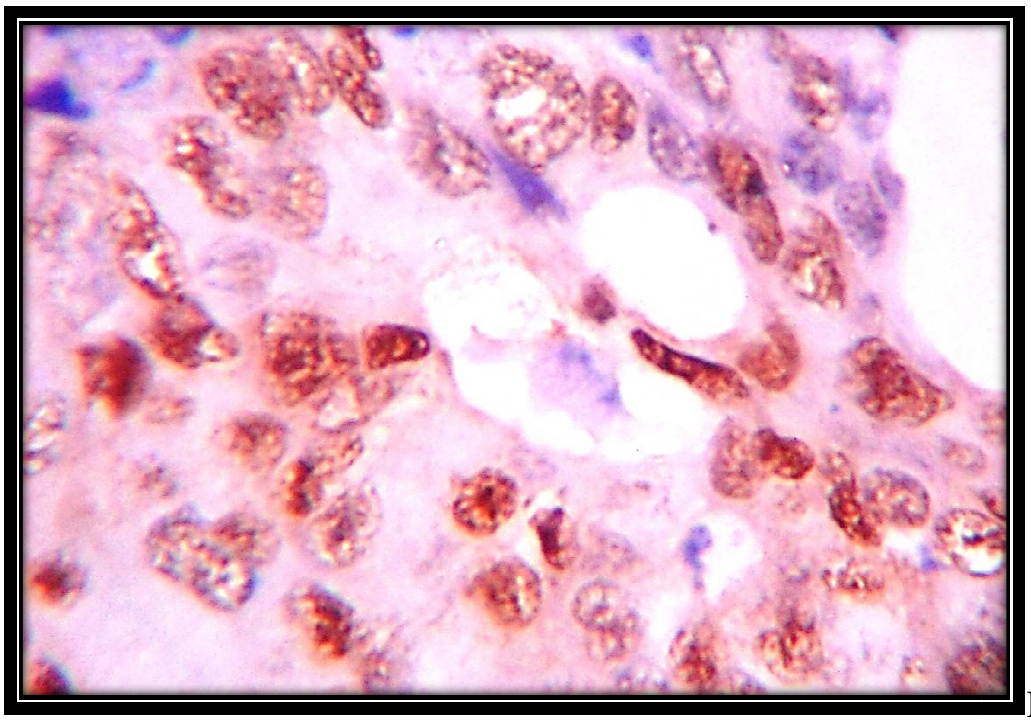


FIG 23: Immunohistochemistry for Estrogen receptor showing strong nuclear positivity in tumour cells. x400 (1574/12).

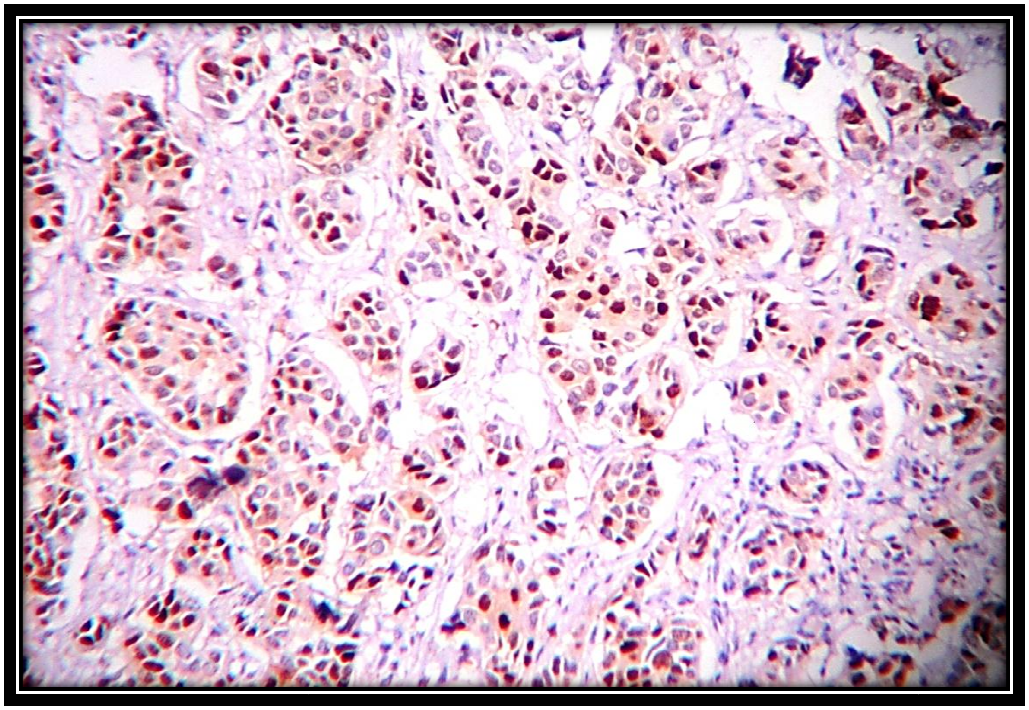


FIG 24: Immunohistochemistry for Progestrone receptor showing strong nuclear positivity in tumour cells. x100 (1574/12).

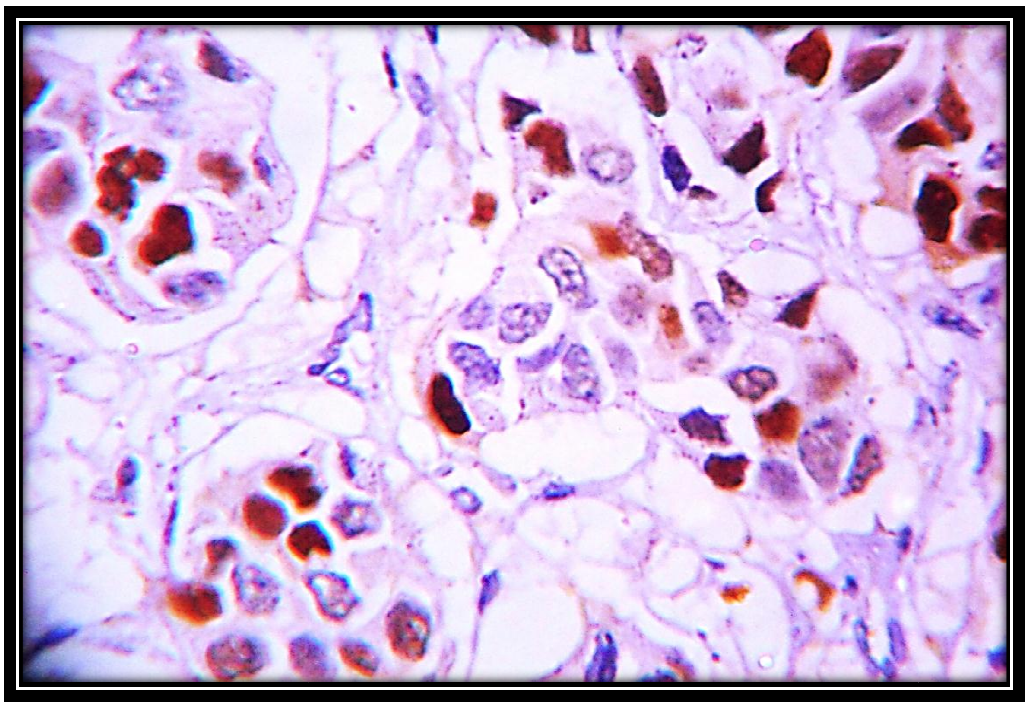


FIG 25: Immunohistochemistry for Progestrone receptor showing strong nuclear positivity in tumour cells. x400 (1574/12).

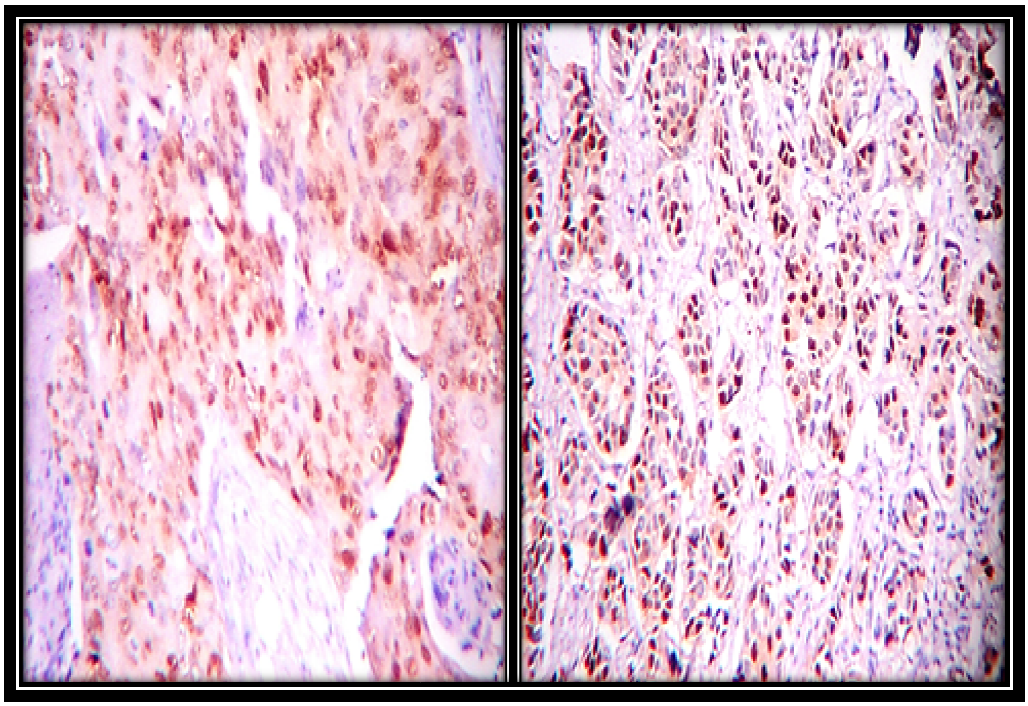


FIG 26: ER and PR positive. x100 (1574/12).

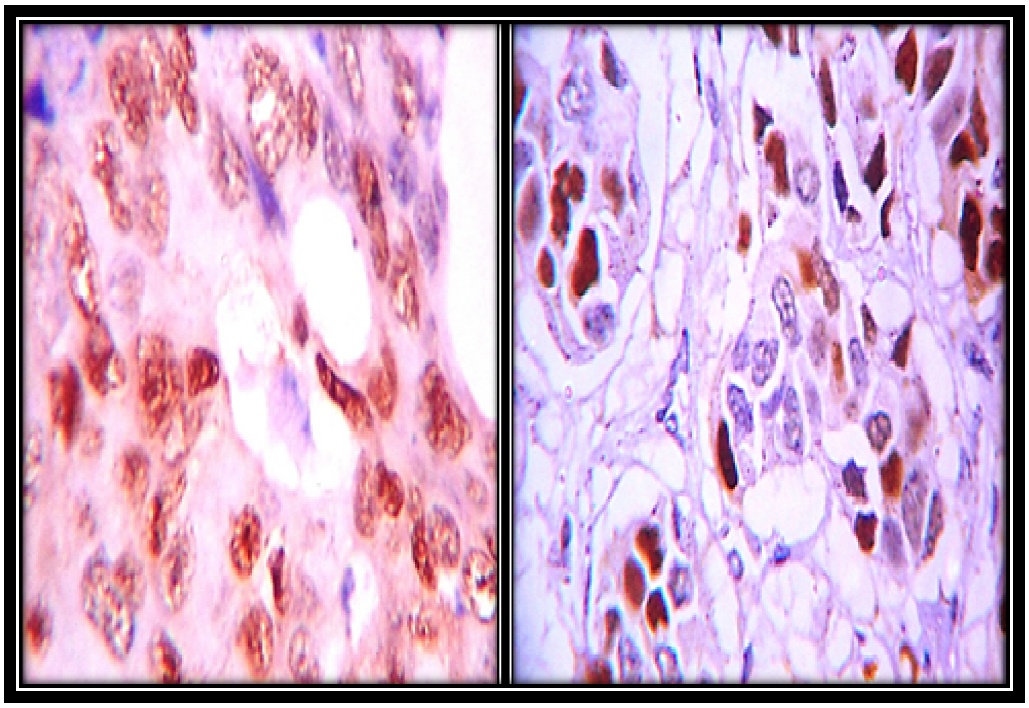


FIG 27: ER and PR positive. x400 (1574/12).

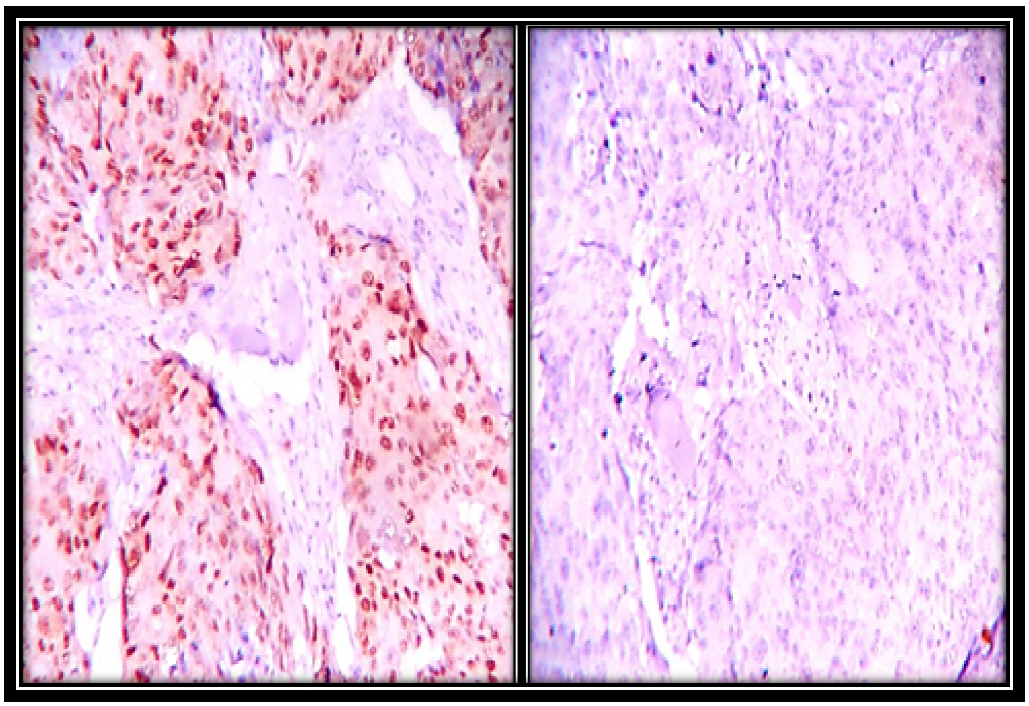


FIG 28: ER positive, PR negative. x100 (1385 /12).

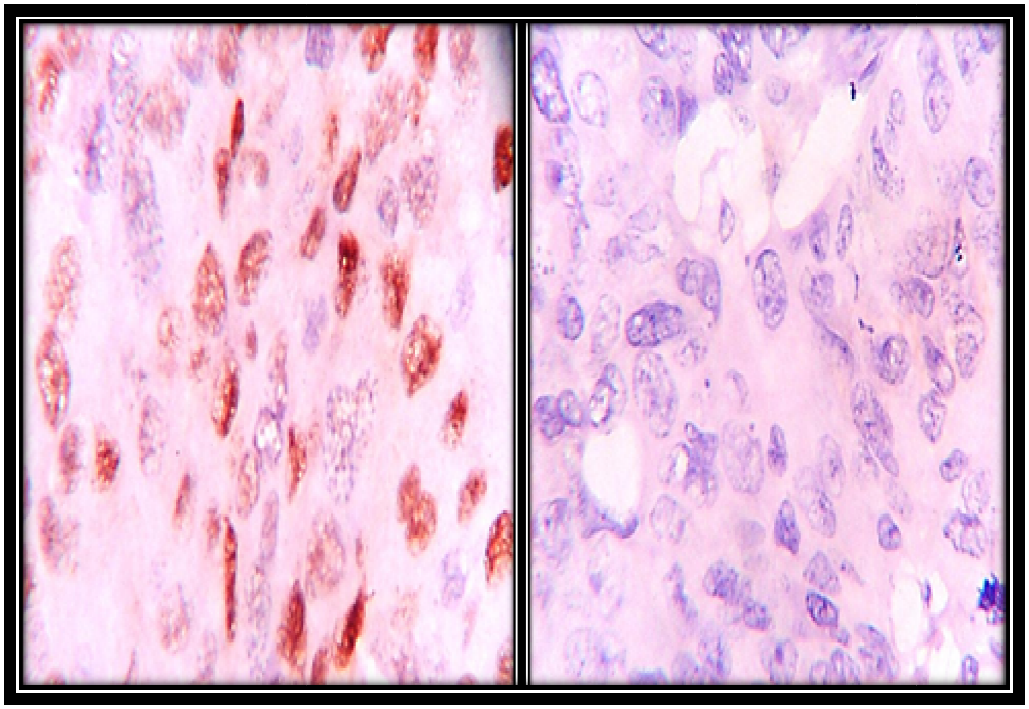


FIG 29: ER positive, PR negative. x400 (1385/12).

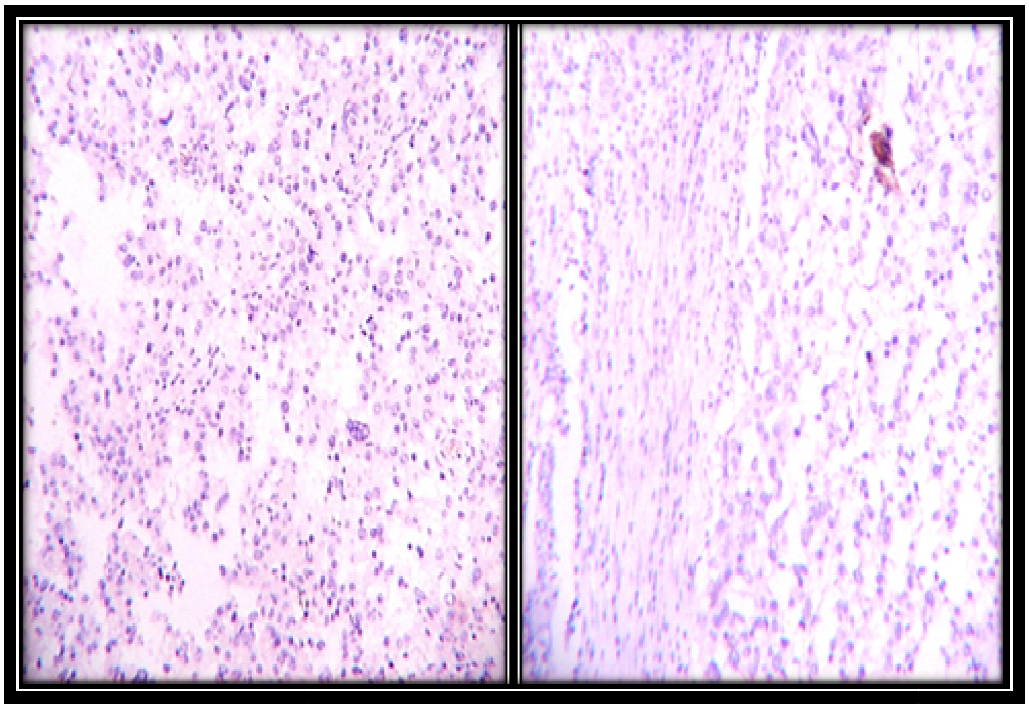


FIG 30: ER, PR negative. x100 (2120/12).

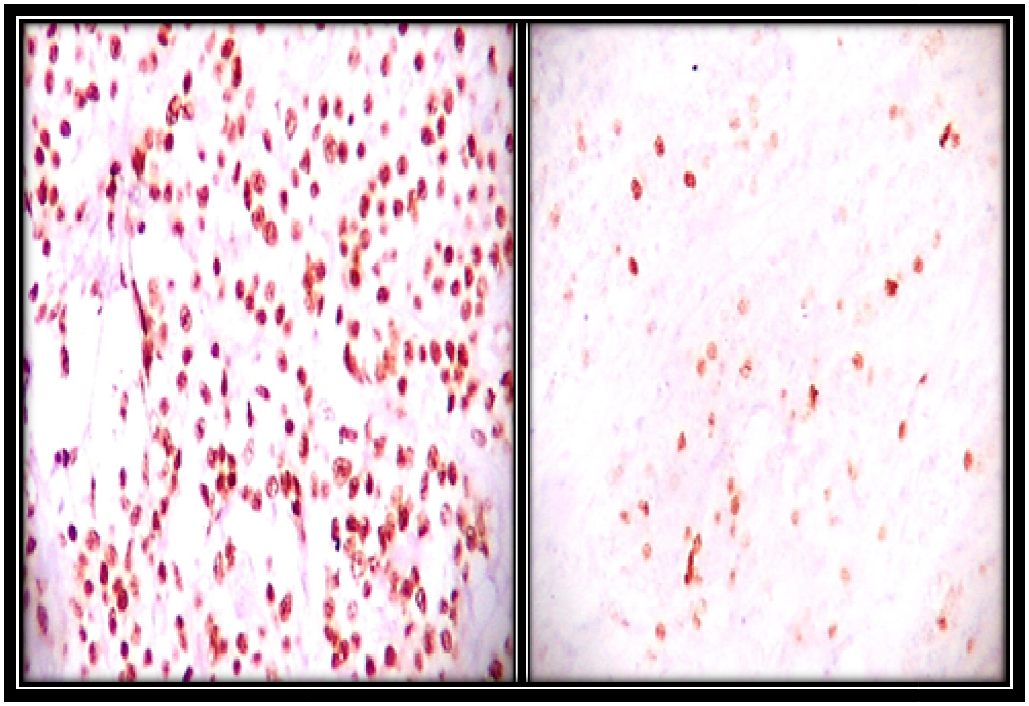


FIG 31: Lobular Carcinoma showing ER Positivity with focal PR Positivity. x100 (4130/11).

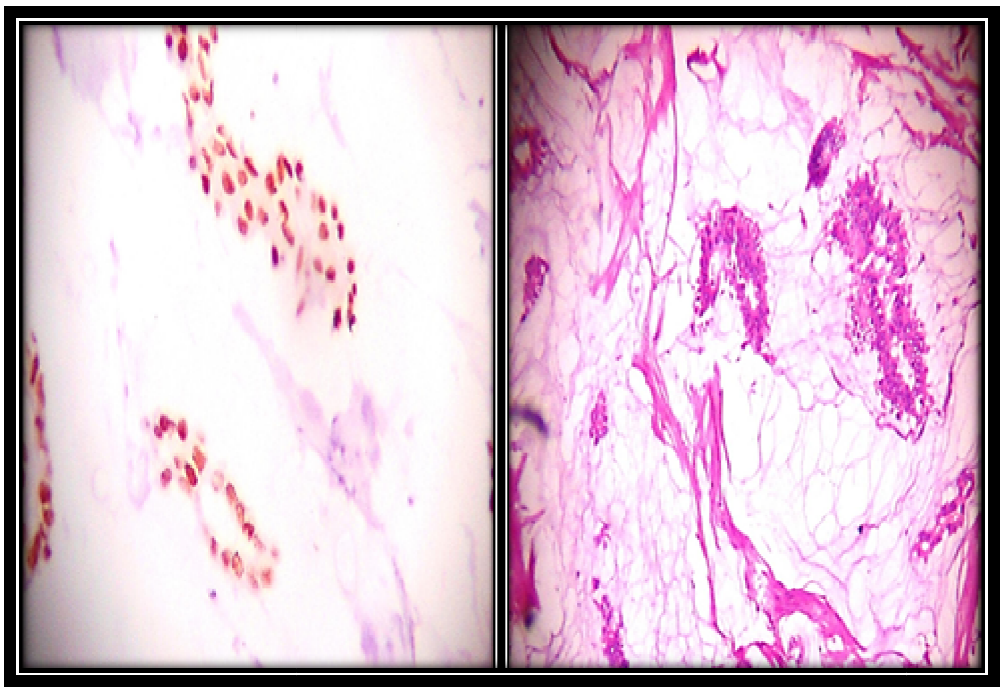


FIG 32: Mucinous carcinoma - ER Positive, PR Negative.

x100 (3899/10).

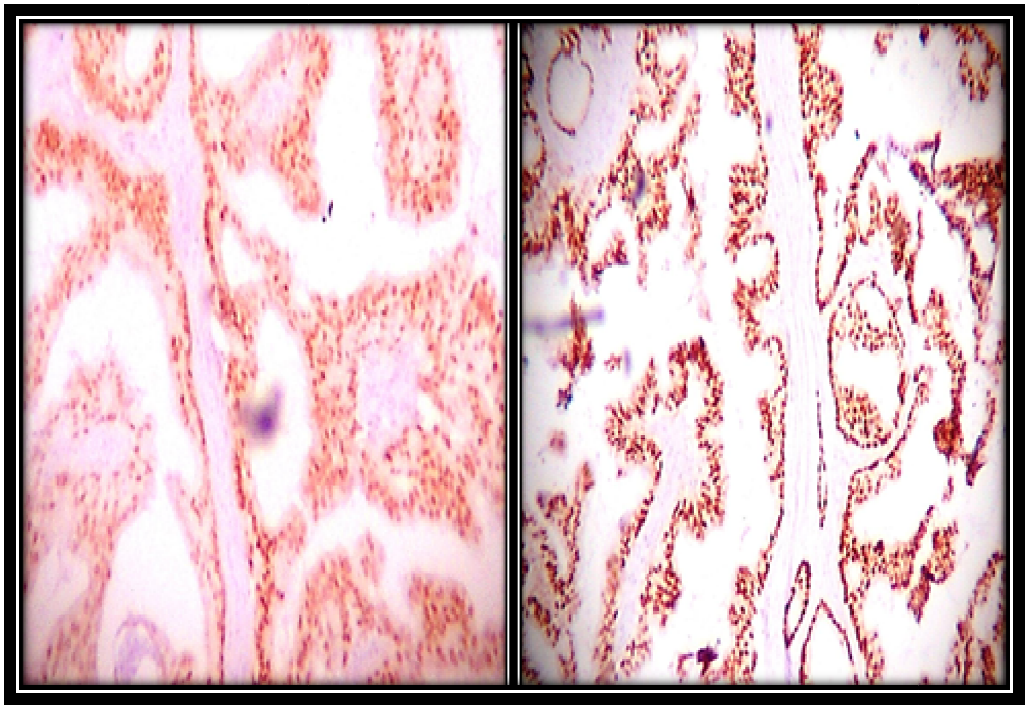


FIG 33: Papillary carcinoma showing strong ER and PR positivity. x100 (2893/10).

ANNEXURE I

PROFORMA

Name:

Age:

Sex:

Unit:

IP No:

HPE No:

Menopausal status:

Clinical Diagnosis:

Breast: Right / Left

Specimen (Type of Mastectomy):

Past History: Trucut or Lumpectomy done if any:

Macroscopic Examination:

Specimen Size:

Skin and Nipple:

Tumour Site (Quadrant involved):

Tumour Size:

Consistency:

Tumour Margins: Circumscribed / Infiltrative

Posterior Margin:

Lymph node:

Number:

Size (Largest):

Microscopic Examination:

Histopathological Diagnosis:

Skin: Free / Involved

Nipple: Free / Involved

Muscle: Free / Involved

Posterior Surgical Margin: Free / Involved

LYMPH NODES:

Total No:

No. of nodes involved:

Other findings:

Histological Grade:

Hormone Receptor Study:

ER status if done: Positive / Negative

PR status if done: Positive / Negative

ANNEXURE II

WHO CLASSIFICATION OF TUMOURS OF THE BREAST (2003):

- **Epithelial Tumours:**
- Invasive Ductal carcinoma, Not otherwise specified 8500/3
- Mixed type carcinoma
- Pleomorphic carcinoma 8022/3
- Carcinoma with osteoclastic giant cells 8035/3
- Carcinoma with choriocarcinomatous features
- Carcinoma with melanotic features
- Invasive Lobular carcinoma 8520/3
- Tubular Carcinoma 8211/3
- Invasive Cribriform Carcinoma 8201/3
- Medullary Carcinoma 8510/3
- **Mucinous Carcinoma and other tumours with abundant mucin:**

  Mucinous Carcinoma 8480/3

  Cysadenocarcinoma and Columnar cell Mucinous Carcinoma 8480/3

  Signet ring cell Carcinoma 8490/3
- **Neuroendocrine Tumours:**

  Solid Neuroendocrine Carcinoma

  Atypical Carcinoid tumour 8249/3

  Small cell Carcinoma 8041/3

  Large cell Neuroendocrine Carcinoma 8013/3
- Invasive Papillary Carcinoma 8503/3
- Invasive Micropapillary Carcinoma 8507/3

- Apocrine Carcinoma 8401/3
- **Metaplastic Carcinomas** 8575/3

  Pure epithelial Metaplastic Carcinomas 8575/3

  Squamous cell Carcinoma 8070/3

  Adenocarcinoma with spindle cell metaplasia 8572/3

  Adenosquamous Carcinoma 8560/3

  Mucoepidermoid Carcinoma 8430/3

  Mixed epithelial / mesenchymal Carcinomas 8575/3
- Lipid-rich Carcinoma 8314/3
- Secretory Carcinoma 8502/3
- Oncocytic Carcinoma 8290/3
- Adenoid Cystic Carcinoma 8200/3
- Acinic Cell Carcinoma 8550/3
- Glycogen-rich clear cell Carcinoma 8315/3
- Sebaceous Carcinoma 8410/3
- Inflammatory Carcinoma 8530/3
- Lobular Neoplasia
- Lobular Carcinoma in situ 8520/2
- **Intraductal proliferative lesions:**

  Ductal hyperplasia

  Flat epithelial atypia

  Atypical ductal hyperplasia

  Ductal carcinoma in situ 8500/2
- Microinvasive Carcinoma

- **Intraductal Papillary neoplasms:**

Central papilloma	8503/0
Peripheral papilloma	8503/0
Atypical papilloma	
Intraductal papillary carcinoma	8503/2
Intracystic papillary carcinoma	8504/2

- **Adenomas:**

Tubular adenoma	8211/0
Lactating adenoma	8204/0
Apocrine adenoma	8401/0
Pleomorphic adenoma	8940/0
Ductal adenoma	8503/0

- **Myoepithelial lesions:**

Myoepitheliosis	
Adenomyoepithelial adenosis	
Adenomyoepithelioma	8983/0
Malignant myoepithelioma	8982/3

- **Mesenchymal Tumours:**

Hemangioma	9120/0
Angiomatosis	
Hemangiopericytoma	9150/1
Pseudoangiomatous stromal hyperplasia	
Myofibroblastoma	8825/0
Fibromatosis	8821/1
Inflammatory myofibroblastic tumour	8825/1

Lipoma	8850/0
Agiolipoma	8861/0
Granular cell tumour	9580/0
Neurofibroma	9540/0
Schwannoma	9560/0
Angiasarcoma	9120/3
Liposarcoma	8850/3
Rhabdomyosarcoma	8900/3
Osteosarcoma	9180/3
Leiomyoma	8890/0
Leiomyosarcoma	8890/3

- **Fibroepithelial Tumours:**

Fibroadenoma	9010/0
Phyllides tumour	9020/1
Benign	9020/0
Borderline	9020/1
Malignant	9020/3
Periductal stromal sarcoma, low grade	9020/3
Mammary Hamartoma	

- **Tumours of the nipple:**

Nipple adenoma	8506/0
Syringomatous adenoma	8407/0
Paget's disease of the nipple	8540/3

- **Malignant Lymphoma:**

Diffuse large B-cell Lymphoma	9680/3

Burkitt Lymphoma	9687/3
Extranodal marginal zone Lymphoma of MALT type	9699/3
Follicular Lymphoma	9690/3

- Metastatic tumours
- **Tumours of the male breast:**

Gynacomastia	
InvasiveCarcinoma	8500/3
In situ Carcinoma	8500/2

ANNEXURE – III

H &E STAINING PROCEDURE

1. Bring the sections to water.
2. Stain with Harris's hematoxylin for 15 minutes.
3. Rinse in tap water.
4. Differentiate in acid alcohol until only nuclei remain blue.
5. Wash in tap water very briefly.
6. Dip in ammonia water (for 10-20 seconds) saturated lithium carbonate until sections are bright blue.
7. Wash in running tap water for 10-20 minutes.
8. Stain with eosin for 2 minutes.
9. Dehydrate in 95% alcohol.
10. Dehydrate in Absolute alcohol.
11. Clearing in Xylene – 2 changes.
12. Mount in DPX mountant.

Immunohistochemistry for Hormone receptor study

Staining procedure:

1. Rehydrate tissue slides.
2. Antigen retrieval is performed by pressure cooker method.
3. Rinse in buffer for 3 minutes.
4. Apply Primary antibody and incubate for 1 hour.
5. Rinse in buffer for 3 minutes.
6. Apply anti-polyvalent HRP polymer and incubate for 30 minutes at room temperature.
7. Rinse 3 minutes in buffer.
8. Rinse in distilled water.
9. Add 1 drop (40-50microlitre) of DAB chromogen concentrate to each one ml vial, mix by swirling, apply to slides and wait for 5 minutes.
10. Rinse in distilled water.
11. Apply DAB Chromogen/substrate mixture and incubate for 5 minutes.
12. Rinse 3 times in buffer
13. Apply hematoxylin stain and incubate for 5 minutes.
14. Rinse 3 times in distilled water
15. Take the sections to running water for bluing.
16. Dehydrate, clear and mount.

ANNEXURE IV

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ABBREVIATIONS

ICMR	-	Indian Council Of Medical Research
PBCR	-	Population Based Cancer Registry
F	-	Female
PrM	-	Premenopausal
PM	-	Postmenopausal
R	-	Right
L	-	Left
MRM	-	Modified Radical Mastectomy
SM	-	Simple Mastectomy
U/O	-	Upper Outer
L/O	-	Lower Outer
L/I	-	Lower Inner
SA	-	Sub Areolar
ALL	-	All Quadrant
N	-	Normal
P	-	Puckered
U	-	Ulcerated
Nod	-	Nodular
Ret	-	Retracted
PG	-	Proliferative Growth

ALND	-	Axillary lymph node dissection
LN	-	Lymph Node
MET LN	-	Lymph Node with Metastasis
SBR	-	Scarff Bloom Richardson
ER	-	Estrogen Receptor
PR	-	Progesterone Receptor
DFS	-	Disease Free Survival
OS	-	Overall Survival
IDC	-	Invasive Ductal Carcinoma
IDC - NOS	-	Invasive Ductal Carcinoma, not otherwise specified
IDC-PD	-	Invasive Ductal Carcinoma with Paget's Disease
IDC-FCD	-	Invasive Ductal Carcinoma With Fibrocystic Disease
IDC-FA	-	Invasive Ductal Carcinoma With Fibroadenoma
ILC	-	Invasive Lobular Carcinoma
MC	-	Mucinous Carcinoma
ICC	-	Invasive Cribriform Carcinoma
PC	-	Papillary Carcinoma
MIPC	-	Micropapillary Carcinoma
MEC	-	Medullary Carcinoma
MPC	-	Metaplastic Carcinoma
PT	-	Phyllides Tumour
CSP-M	-	Malignant Cystosarcoma Phylloides

Ref. No. 6087/E4/3/2011

Govt.Rajaji Hospital,Madurai.20.
Dated: 14.12.2011

Sub: Establishment-Govt. Rajaji Hospital, aMadurai-20-
Ethics committee-Meeting Agenda-communicated-regarding.

The next Ethics Committee meeting of the Govt. Rajaji Hospital, Madurai was held at 11.00 Am to 1.00 Pm on Thursday the 27th Oct 2011 at the Dean's Chamber, Govt. Rajaji Hospital, Madurai. The following members of the committee have attend the meeting.

1.Dr.V. Ramanujam, M.D., D.P.M.,	M.S, i/c Govt.Rajaji Hospital,Madurai.	Convenor
2.Dr.N.Vijayasankaran,M.ch(Uro.) 094-430-58793 0452-2584397	Sr.Consultant Urologist Madurai Kidney Centre, Sivagangai Road,Madurai	Chairman
3. Dr.P.K. Muthu Kumarasamy, M.D., 9843050911	Professor & H.O.D of Medical, Oncology(Retired)	Member Secretary
4.Dr.T.Meena,MD 094-437-74875	Professor of Physiology, Madurai Medical College	Member
5.Dr.Moses K.Daniel MD(Gen.Medicine) 098-421-56066	Professor of Medicine Madurai Medical College	Member
6.Dr.M.Gobinath,MS(Gen.Surgery)	Professor of Surgery Madurai Medical College	Member
7.Dr.S. Dilshadh, MD(O&G)	Professor of OP&Gyn Madurai Medical College	Member
8.Dr.S.Vadivel Murugan., M.D. 097-871-50040	Professor of Medicine Madurai Medical College	Member
9.Shri.M.Sridher,B.sc.B.L. 099-949-07499	Advocate, 623-B.II.Floor,East II Cross, K.K.Nagar,Madurai.20.	Member
10.Shri.O.B.D.Bharat,B.sc., 094-437-14162	Businessman Plot No.588, K.K.Nagar,Madurai.20.	Member
11.Shri. S.sivakumar,M.A(Social) Mphil 093-444-84990	Sociologist, Plot No.51 F.F, K.K Nagar, Madurai.	Member

Following projects were approved by the committee.

Sl. No	Name of P.G.	Course	Name of the Project	Remarks
1.	Dr. Mercy Swamidoss,	PG, M.D (path)	Clinicopathologic correlations in neoplastic and non-neoplastic endometrial lesions.	Approved
2.	Dr. B. Shobana	PG, M.D (path) MMC	Clinicopathologic Correlations of breast lesions with ER and PR assays in selected patients.	Approved
3.	Dr. R. Sivaelangovan	PG, M.D (path)	Clinicopathologic and cytologic correlations of head and neck lesions.	Approved
4.	Dr.A. Divya	PG, M.D (path)	Clinicopathologic correlations of colorectal neoplasms.	Approved
5.	Dr. N. Muthusamy	PG, M.S (genl surg)	Various modalities of treatment in liver abscesses.	Approved
6.	Dr. R. Kalpana	PG, M.S (genl surg)	Various modalities of treatment in haemarrhoids .	Approved
7.	Dr. T. Ashok Kumar	PG, M.S (genl surg)	Various techniques of umbilical hernia repair.	Approved
8.	Dr. A. Ranjani	PG, M.S (genl surg)	Complication of laparoscopic procedures.	Approved
9.	Dr A. Meenakshi Sundaram	PG, M.S (genl surg)	Clinico-pathologic study and treatment of sino-nasal masses.	Approved
10.	Dr. N. Prasanna Venkateshan	PG, M.S (ortho)	Functional outcome after bipolar hemiarthroplasty for unstable femoral intertrochanteric fractures in elderly patients.	Approved
11.	Dr.S. Siva Swaminathan	PG, M.S (ortho)	Congenital proximal radioulnar synostosis treated with derotation osteotomy through the synostotic mass – analysis of results.	Approved
12.	Dr. T. Arun Sam	PG, M.S (ortho)	Functional outcome of clavicular fractures treated with plate osteosynthesis.	Approved
13.	Dr.P. Arun Anand	PG, M.S (ortho)	Functional and radiologic outcome of unstable acetabular fractures treated with 'single approach'.	Approved
14.	J. Asnet Mary	Research Associate (Biotech)	Identification and characterization of biomolecules involved in dengue virus-vector-host interactions.	Approved
15.	A. Britto	PG, M.Sc (Nursing; med-surg)	Effectiveness of planned teaching strategies on knowledge of practice on effects of chemotherapy among patients attending oncology outpatient department.	Approved

16.	Dr. Virgin Joena	PG, MD(gen Med)	Prevalance of periodontitis and missing teeth in a group of diabetic patients as compared with a group of healthy patients.	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain Confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution to Government.
2. She/He should inform the institution Ethical Committee in case of any change of study procedure site and investigation or guide.
3. She/He should not deviate for the area of the work for which applied for Ethical clearance.

She/He should inform the IEC immediately, in case of any adverse events pr Serious adverse reactions.

4. She/he should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and apply for if any Extension of time is required She should apply for permission again and do the work.
6. She/He should submit the summary of the work bio the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the word or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

DEAN

10/12/19

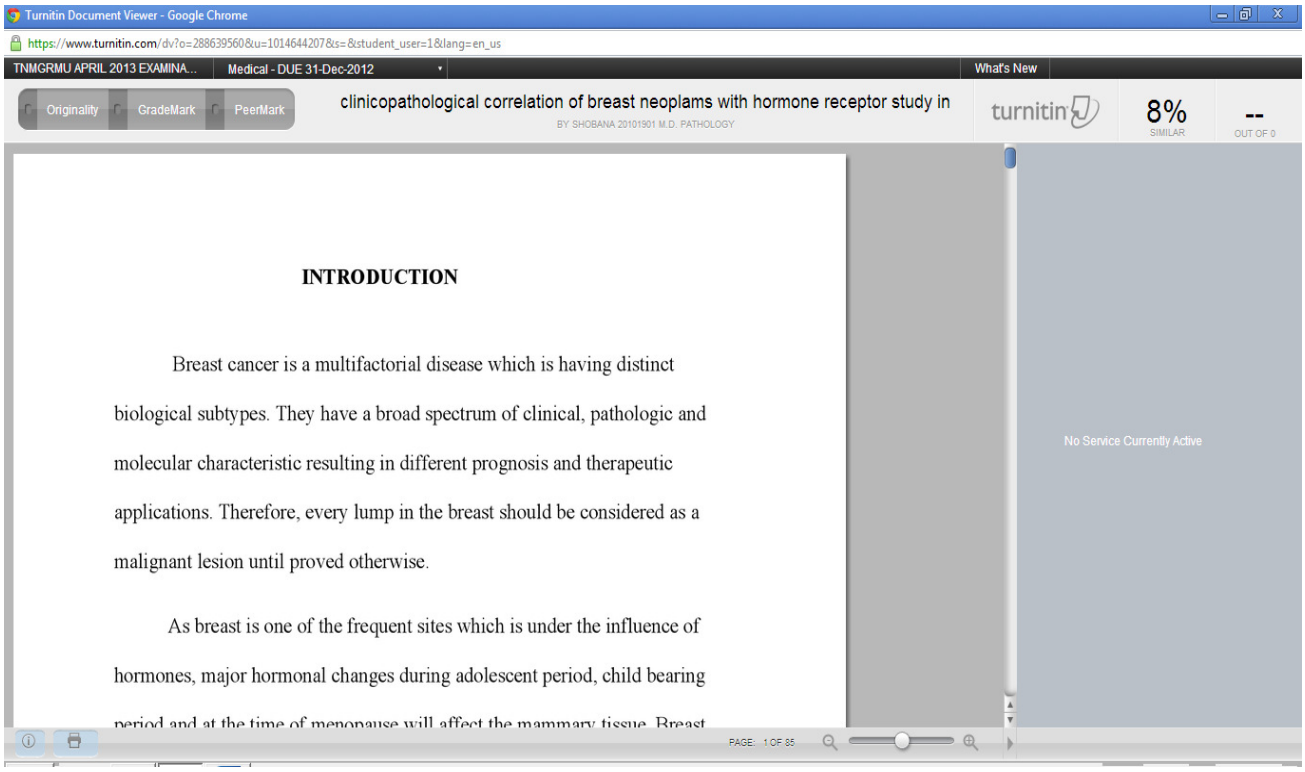
To

All the above members and Head of the Departments concerned.

All the Applicants.

ANNEXURE VII

ANTI – PLAGIARISM CERTIFICATE



ANNEXURE - V

MASTER CHART

S.No	Name	Age	Sex	Menopause	HPE NO	Specimen	side	Tumour		Nipple	Skin	Consistency	LN(no)	HP Diagnosis		Histolo-gical Grade
								site	Size(cm)					Tumour	MET LN	
1	VELAMMAL	50	F	PM	1929/10	MRM	R	U/O	3.5X3X2	N	_	FIRM	5	IDC	2	II
2	AMEENA BEEVI	55	F	PM	1988/10	MRM	L	U/O	5X4X3	N	P	FIRM	5	IDC	1	II
3	AMIRTHAM	30	F	PrM	2081/10	MRM	L	U/O	4x3x2	N	_	FIRM	6	IDC	5	III
4	IRULAYEE	79	F	PM	2108/10	MRM	L	SA	7x6x4.5	N	_	FIRM	10	IDC	9	I
5	MUNIYAMMAL	31	F	PrM	2120/10	MRM	L	U/O	2X2X1	N	_	FIRM	8	IDC	_	I
6	LAXMI	50	F	PM	2141/10	MRM	R	U/O	2x1.5x1	N	_	FIRM	7	IDC	_	III
7	MARIAMMAL	43	f	PrM	2161/10	MRM	R	U/I	3X2X1	N	Nod	FIRM	15	IDC	4	II
8	SHANMUGAVALLI	35	F	PrM	2267/10	MRM	L	SA	3X2X1	N	_	FIRM	4	IDC	2	II
9	ARUMUGATHAMMAL	60	f	PM	2458/10	MRM	L	U/O	8X4X3	N	_	FIRM	13	IDC	13	III
10	ANNAMMAL	45	F	PrM	2476/10	MRM	R	SA	3x2x1.5	N	_	FIRM	6	IDC	1	II
11	TAMILSELVI	47	F	PrM	2710/10	MRM	L	U/O	9X8X3	N	_	FIRM	9	IDC	2	III
12	KATHAYEE	45	F	PrM	2714/10	MRM	L	U/O	4X3X2	N	_	FIRM	5	IDC	1	II
13	VALLIAMAL	65	F	PM	2765/10	MRM	R	SA	6X5X3	U	U	FIRM	3	IDC	2	II
14	UNNAMALAI	57	F	PM	2767/10	MRM	L	U/I	6X4X2	N	_	FIRM	6	IDC	4	II
15	THANGAMMAL	43	F	PrM	2772/10	MRM	R	L/I	10X9X4	N		FIRM	_	CSP-M	_	_
16	SUMATHY	24	F	PrM	2832/10	MRM	L	U/O	10X8X3	N	_	FIRM	6	IDC	5	III
17	THANGATHAI	70	F	PM	2893/10	MRM	R	L/I	5X4X3	N	_	FIRM	7	PC	6	_
18	MURUGESWARI	61	F	PM	2934/10	MRM	L	U/O	4X3X2	N	_	FIRM	6	IDC	2	II
19	SEETHALAXMI	38	F	PrM	3041/10	MRM	L	U/I	12x8x3	N	_	FIRM	9	IDC	4	III
20	ABIRAMI	38	F	PrM	3060/10	MRM	L	U/O	4x3x2.5	N	_	FIRM	20	IDC	20	II
21	JOTHI	70	F	PM	3181/10	MRM	R	SA	2X2X1	N	_	FIRM	7	IDC	_	I
22	PREMA	54	F	PM	3487/10	MRM	L	U/O	6x5x5	N	_	FIRM	5	IDC-PD	3	II
23	PASUPATHY	40	F	PrM	3561/10	MRM	L	SA	4x3.5x3	N	_	FIRM	14	IDC	11	III
24	SAMSATH	47	F	PrM	3570/10	MRM	R	U/O	6x4x4	Ret	U	FIRM	7	IDC	6	II
25	LAXMI	50	F	PM	3618/10	MRM	R	U/O	3.5x3x2	N	_	FIRM	8	IDC	5	II
26	LAXMI	68	F	PM	3620/10	MRM	R	L/O	3x2x2	N	_	FIRM	7	IDC	5	II
27	JAYANTHI	45	F	PrM	3661/10	MRM	L	SA	5x4x2	N	_	FIRM	7	IDC	7	II
28	SHANTHADEVI	58	F	PM	3663/10	MRM	L	U/O	2X2X1	N	_	FIRM	3	IDC	_	I
29	ANDAL	48	F	PrM	3727/10	MRM	L	U/I	6x5x4	N	_	FIRM	4	IDC	4	III
30	ANGAMMAL	40	F	PrM	3766/10	MRM	L	U/O	5x3x2	N	P	FIRM	2	IDC	2	II
31	RAMALAXMI	40	F	PrM	3781/10	MRM	L	U/O	3x3x2	N	_	FIRM	4	IDC	1	II
32	VASANTHA	47	F	PrM	3877/10	MRM	L	L/O	5x4x3	N	_	FIRM	5	IDC	1	II

33	PAPPU	45	F	PrM	3881/10	MRM	R	U/O	5x4x3	N	P	FIRM	6	IDC	6	III
34	PANDIAMMAL	42	F	PrM	3886/10	MRM	L	SA	7.5x5x3	N	_	FIRM	6	IDC	6	III
35	LAXMI	45	F	PrM	3889/10	MRM	L	U/O	5x3x2	N	_	FIRM	3	IDC	1	II
36	MUNIYAMMAL	55	F	PM	3899/10	MRM	L	U/I	5x4x3	N	P	gelatinous	6	MC	2	_
37	DHAVAMANI	60	F	PM	114/11	MRM	L	L/O	7X5X3	N	P	FIRM	4	IDC	4	III
38	ANGAMMAL	77	F	PM	147/11	MRM	R	U/O	6X6X5	U	PG	FIRM	3	IDC-PD	2	III
39	SHAKILABEGUM	43	F	PrM	224/11	MRM	L	U/O,U/I	9X8X5.5	N	_	FIRM	5	IDC	5	III
40	MEERA	57	F	PM	255/11	MRM	R	U/O	2X2X1	N	_	FIRM	3	IDC	_	I
41	NACHAMMAL	40	F	PrM	265/11	MRM	R	SA	6X5X3	R	_	FIRM	9	IDC	3	II
42	MALLIKA	50	F	PM	280/11	MRM	R	U/O	2X2X1	N	_	FIRM	5	IDC	_	I
43	SAROJA	78	F	PM	373/11	MRM	R	U/O	9x4x2.5	N	_	FIRM	9	IDC	2	II
44	MAHALAXMI	40	F	PrM	517/11	MRM	R	SA	2X2X1	N	_	FIRM	4	IDC	_	I
45	RAJAMMAL	50	F	PM	627/11	MRM	R	U/I	5X4X4	N	_	gelatinous	7	MC	1	_
46	LAX,MI	45	F	PrM	669/11	MRM	L	U/O	4X3X2	N	_	FIRM	3	IDC	2	II
47	DEVI	45	F	PrM	709/11	MRM	L	U/O,U/I	9x8x4	N	_	FIRM	9	IDC	8	III
48	POOMADEVI	61	F	PM	737/11	MRM	R	U/O	2X2X1	N	_	FIRM	3	IDC	_	I
49	JEYA	45	F	PrM	849/11	MRM	L	L/O	2X2X1	N	_	FIRM	6	IDC	_	II
50	AATHILAXMI	35	F	PrM	885/11	MRM	R	L/O	4.5x2.5x2	N	_	FIRM	4	IDC	2	I
51	RAJALAXMI	55	F	PM	1030/11	MRM	R	U/O	5x3.5x3	N	_	FIRM	4	IDC	2	II
52	PAPPAMMAL	64	F	PM	1074/11	MRM	R	U/O	3x2x1	N	_	FIRM	2	IDC	2	II
53	PADMA	45	F	PrM	1075/11	MRM	R	U/O	7x4x2	Ret	_	FIRM	5	IDC	5	III
54	FATHIMA BEEVI	69	F	PM	1098/11	MRM	L	U/O	4x2.5x2	N	_	FIRM	9	IDC	2	II
55	CHIBA	30	F	PrM	1152/11	MRM	L	U/O,U/I	8x6x3	N	_	FIRM	4	IDC	2	II
56	AMARAVATHY	42	F	PrM	1257/11	MRM	R	U/O	10X7X4	Ret	_	FIRM	16	IDC	10	III
57	ARAYEE	50	F	PM	1258/11	MRM	L	U/O	6X3X2	N	_	FIRM	5	IDC	5	III
58	MUTHURAKKU	40	F	PrM	1284/11	MRM	L	SA	3x3x2	N	_	FIRM	1	IDC-,FCD	1	II
59	RAJESWARI	53	F	PM	1294/11	MRM	L	SA	5x3x2	Ret	_	FIRM	5	IDC	4	III
60	ALEEMA BEEVI	42	F	PrM	1389/11	MRM	R	U/O,SA	9x8x6	N	_	FIRM	4	IDC	4	III
61	KASIAMMAL	70	F	PM	1418/11	MRM	R	U/O	5x5x3.5	N	Nod	FIRM	8	IDC	6	III
62	MARIAMMAL	40	F	PrM	1569/11	MRM	L	L/I	12X10X8	N	Nod	FIRM	_	CSP-M	_	_
63	PANCHAVARNAM	30	F	PrM	1664/11	MRM	L	U/I	2X2X1	N	_	FIRM	6	IDC	_	I
64	KALYANI	37	F	PrM	1680/11	MRM	R	U/O,SA	5.5X5X1.5	N	_	FIRM	2	IDC	2	III
65	SABITHA	45	F	PrM	1686/11	MRM	L	U/O	3X2X1	N	_	FIRM	12	IDC	2	II
66	GNANASUNDARI	45	F	PrM	1733/11	MRM	R	U/O	6x4.5x3	N	_	FIRM	12	IDC	12	III
67	BANUMATHY	28	F	PrM	1777/11	MRM	L	U/O,SA	4x3.5x1.5	N	_	FIRM	5	IDC	1	II
68	PITCHAIAMMAL	55	F	PM	1827/11	MRM	L	L/O	2X2X2	N	_	FIRM	5	IDC	_	I
69	KALIAMMAL	60	F	PM	1828/11	MRM	L	SA	4x3x1	N	_	FIRM	3	IDC	3	II

70	ESWARI	41	F	PrM	1996/11	MRM	R	U/O	9x5x1.5	N	_	FIRM	1	IDC	1	II
71	PARANJOTHI	60	f	PM	2012/11	MRM	L	U/O.SA	6x4x3.5	Ret	_	FIRM	6	IDC	5	III
72	MARIAMMAL	49	F	PrM	2125/11	MRM	L	U/O	1.5x1x1	N	_	FIRM	10	IDC	_	I
73	KARPAGAVALLI	28	F	PrM	2127/11	MRM	L	U/O	10x9x5	N	_	FIRM	16	IDC	16	II
74	RANI	40	F	PrM	2236/11	MRM	L	U/O	4x3x2	N	U	FIRM	5	IDC	3	III
75	MUTHULAXMI	29	F	PrM	2237/11	MRM	R	U/O	7x4.5x2	N	_	FIRM	4	IDC	4	III
76	ATHIJABEGUM	37	F	PrM	2260/11	MRM	L	U/I	2X2X1	N	_	FIRM	8	IDC	_	I
77	LATHAMANGESWARI	53	F	PM	2273/11	MRM	L	SA	6x3.5x2	N	_	FIRM	6	IDC	6	III
78	KALIMUTHU	50	F	PM	2310/11	MRM	R	U/O	4.5x3.5x3	N	_	FIRM	6	IDC	4	II
79	SHANTHI	35	F	PrM	2311/11	MRM	R	SA	2.5x2x2	N	_	FIRM	4	IDC	2	III
80	VELAMMAL	37	F	PrM	2420/11	MRM	R	SA	4x3x2	N	_	FIRM	9	IDC	8	III
81	LALITHA	30	F	PrM	2440/11	MRM	L	L/O	4x3x2	N	_	FIRM	8	IDC	8	II
82	GORIJAN	37	F	PrM	2481/11	MRM	L	U/O,SA	4x3.5x3	N	_	FIRM	12	IDC	3	II
83	RAJAMMAL	50	F	PM	2551/11	MRM	L	L/O	5x2.5x2	N	_	FIRM	7	IDC	3	II
84	ARUMUGAM	40	F	PrM	2560/11	MRM	L	SA	8x5x2.5	N	_	FIRM	8	IDC	3	II
85	MARIYAM BEEVI	55	F	PM	2629/11	MRM	L	U/O	5x3.5x3	N	_	FIRM	5	IDC	1	II
86	VIJAYALAXMI	43	F	PrM	2633/11	MRM	L	L/O	3x2.5x2	N	_	FIRM	8	IDC	1	II
87	MUTHU	43	F	PrM	2660/11	MRM	R	U/O,SA	7x4.5x4	N	_	FIRM	5	IDC	3	III
88	CHITTUPONNU	36	F	PrM	2670/11	MRM	B/L	U/O	4x3x2,1.5	N	_	FIRM	5(2,3)	IDC	2,	II
89	SAVITHRI	46	F	PrM	2791/11	MRM	L	L/O,L/I	7.5x7x4	Ret	U	FIRM	11	IDC	3	II
90	MARIAMMAL	58	F	PM	2831/11	MRM	L	U/O	3.5x3x2.5	N	_	FIRM	_	IDC	_	III
91	PONNAMMAL	63	F	PM	2846/11	MRM	L	SA	4X3.5X2	Ret	_	FIRM	4	IDC	2	II
92	RAMAYEE	55	F	PM	2875/11	MRM	R	U/O,SA	5x4x3	N	_	FIRM	7	IDC	5	III
93	LAXMI	30	F	PrM	2891/11	MRM	L	U/I	2x1.5x1.5	Ret	_	FIRM	10	IDC	_	I
94	SARASWATHY	62	F	PM	2926/11	MRM	L	L/O	8x5x4	N	P	FIRM	7	IDC	7	III
95	PAPAMMAL	65	F	PM	2929/11	MRM	R	U/O	3x3x2	N	_	FIRM	8	IDC	5	II
96	SHANTHI	38	F	PrM	2971/11	MRM	L	U/O,U/I	8x5x2	N	_	FIRM	1	IDC	1	III
97	ALAGAMMAL	49	F	PrM	3014/11	MRM	R	SA	7x5x4	N	Nod	FIRM	8	IDC-PD	8	II
98	NALLAMMAL	60	F	PM	3015/11	MRM	L	U/O,U/I	7.5x7x5	N	U	FIRM	7	IDC-PD	5	III
99	KALA	48	F	PrM	3028/11	MRM	R	U/O,U/I	10x8x5	N	_	FIRM	4	IDC	4	II
100	MUTHAMMAL	40	F	PrM	3089/11	MRM	R	U/O	2X2X1	N	U	FIRM	3	IDC	_	I
101	GOMATHIAMMAL	40	F	PrM	3305/11	MRM	L	L/O	5X4X3	N	_	FIRM	7	MPC	2	_
102	ARAYAMMAL	75	F	PM	3307/11	MRM	L	SA	6X5X4	N	_	FIRM	6	IDC	4	III
103	SHANTHI	38	F	PrM	3329/11	MRM	R	L/I	4X3X2	N	_	FIRM	3	IDC-FCD	2	II
104	MUNIYAMMAL	60	F	PM	3330/11	MRM	R	L/O	5X4X3	N	_	HARD	4	IDC	3	II
105	INDHRANI	55	F	PM	3356/11	MRM	L	U/O	2X2X1	N	_	FIRM	5	IDC	_	I
106	MUTHU	70	F	PM	3373/11	MRM	R	SA	2X2X1	N	_	FIRM	7	IDC	_	I

107	AMSALAXMI	69	F	PM	3428/11	MRM	R	L/O	6X3.5X3	N	P	FIRM	2	IDC	1	II
108	PANDIAMMAL	43	F	PrM	3460/11	MRM	L	L/I	10X8X5	N	_	FIRM	6	IDC	6	III
109	BACKIYAM	70	F	PM	3622/11	SM	R	U/I	12X9X8	N	_	FIRM	_	CSP-M	_	_
110	PAPPA	68	F	PM	3813/11	MRM	L	SA	7X4X2.5	N	_	HARD	4	IDC	2	III
111	DHANALAXMI	40	F	PrM	4009/11	MRM	L	U/O	6X3X2	N	_	FIRM	6	IDC-FCD	2	II
112	SHENBAGAVALLI	45	F	PrM	4037/11	MRM	R	L/O	6X5X4	N	_	FIRM	4	IDC	1	II
113	SUBBAMMAL	45	F	PrM	4130/11	MRM	L	L/O	6X5.5X5	N	P	FIRM	8	ILC	5	_
114	KALIMUTHU	70	F	PM	4316/11	RM	L	L/O	2X2X1	N	P	FIRM	2	IDC	_	I
115	AMSAVALLI	35	F	PrM	4334/11	MRM	L	L/O	2X2X1	N	_	FIRM	15	IDC	_	I
116	INDHRANI	60	F	PM	4355/11	MRM	L	L/I	6X5.5X4	N	_	FIRM	10	IDC	7	III
117	MUNIYAMMAL	65	F	PM	4374/11	MRM	L	U/O	5X4X3	N	_	FIRM	7	IDC	2	II
118	KAMALAM	62	F	PM	8/12	MRM	R	L/O	2X2X1	N	_	FIRM	3	IDC	_	I
119	TAMILARASI	60	F	PM	99/12	MRM	L	U/O	3.5X1.5X1	N	P	FIRM	11	IDC	2	II
120	KULANTHAI SAROJA	57	F	PM	129/12	MRM	L	U/I	2X2X1	N	_	FIRM	4	IDC	_	I
121	GANDHIMATHI	39	F	PrM	166/12	MRM	L	L/O	4X3X1.5	N	_	HARD	11	IDC-FA	8	II
122	PERIAMMAL	55	F	PM	175/12	MRM	L	U/O	6.5X5X4	N	_	HARD	10	IDC	4	III
123	VIJAYA	47	F	PrM	177/12	MRM	R	U/I	2X2X1	N	_	HARD	7	IDC	_	I
124	LAXMI	42	F	PrM	217/12	MRM	R	U/O	5.5X5X4	N	P	HARD	24	IDC	24	III
125	ANGAMUTHU	70	F	PM	320/12	MRM	R	SA	6X5X4	N	P	HARD	17	IDC	2	II
126	LOORDHUMARI	60	F	PM	445/12	MRM	L	SA	6X4X2	N	_	gelatinous	6	MC	2	_
127	MEENATCHI	70	F	PM	543/12	MRM	R	L/I	5X3X2.5	Ret	P	FIRM	3	IDC	2	II
128	SUNDHARI	43	F	PrM	569/12	MRM	L	U/O	4.5x4x3	N	_	FIRM	11	IDC	2	II
129	AROKIAMMAL	55	F	PM	597/12	MRM	L	U/O	3X2X1	N	_	FIRM	11	IDC	11	II
130	AMUDHA	38	F	PrM	744/12	MRM	L	L/O	15X7X6	N	_	FIRM	4	IDC	2	III
131	SHANMUGAVALLI	48	F	PrM	842/12	MRM	R	U/O	3.5X3X2	N	P	FIRM	7	IDC	3	II
132	MARIAMMAL	42	F	PrM	872/12	MRM	L	L/I	6.5x6x4	N	P	FIRM	5	IDC	4	III
133	MURUGESWARI	35	F	PrM	903/12	MRM	R	U/O	6.5X6X5	N	_	FIRM	4	IDC	1	III
134	NEELA	60	F	PM	925/12	MRM	R	U/I	5.5X4.5X4	Ret	P	FIRM	6	ICC	2	_
135	LAXMI	60	F	PM	984/12	MRM	R	U/O	12X9X6	N	_	FIRM	9	IDC	2	II
136	DHANALAXMI	64	F	PM	994/12	MRM	L	SA	8X7X1.5	R	P	Firm	5	IDC	2	II
137	MARIAMMAL	47	F	PrM	1125/12	MRM	L	L/I	8X5X2	N	_	Firm	14	MEC	1	_
138	INDHRANI	55	f	PM	1276/12	MRM	R	U/O	6x5x4	N	_	Firm	9	IDC	4	III
139	NATCHAMMAL	47	F	PrM	1277/12	MRM	L	U/I	4.5X4X3	N	_	Hard	7	IDC	3	II
140	PREMA	39	F	PrM	1366/12	MRM	R	U/I	2X1.5X1	N	_	Hard	5	IDC	_	I
141	PANCHU	35	F	PrM	1384/12	MRM	R	U/O	2X2X1	N	_	Hard	9	IDC	_	I
142	KALIAMMAL	55	F	PM	1385/12	MRM	R	U/I	8X7X5	N	_	Firm	14	IDC	14	III
143	MARIASELVAM	50	F	PM	1520/12	SM	R	U/I	7X6X5.5	U	P	Firm	1	IDC-PD	1	II

144	MANJULA	58	F	PM	1574/12	MRM	L	L/O	2X1.5X1	N	_	Firm	0	IDC	_	I
145	MALLIKA	57	F	PM	1598/12	MRM	R	SA	3.5X3X2	N	_	FIRM	6	IDC	1	II
146	BACKIYALAXMI	35	F	PrM	1621/12	MRM	R	L/O	3X2X1	N	_	Firm	16	IDC	5	II
147	RASATHI	47	F	PrM	1891/12	MRM	R	U/I	4X3X2	U	P	Hard	2	IDC-PD	2	II
148	SUBBURATHINAM	60	F	PM	2069/12	MRM	L	L/I	4X3.5X3	N	_	Firm	2	IDC	2	II
149	ANNAKODI	40	F	PrM	2102/12	MRM	L	U/O,U/I	6X5X3	N	_	Firm	10	IDC	2	II
150	ARUMUGA M	45	F	PrM	2117/12	MRM	R	U/O	5X4X2	N	_	Firm	7	IDC	2	II
151	SAGUBARNISHA	35	F	PrM	2120/12	MRM	R	SA	6x5x4.5	N	_	FIRM	13	IDC	2	II
152	LAXMIKANTHAM	71	F	PM	2156/12	MRM	L	L/O	3x3x2.5	N	_	FIRM	3	MIPC	3	_
153	VEERAMMAL	50	F	PM	2216/12	MRM	L	U/I	6X3X2.5	N	_	FIRM	18	IDC	3	III
154	ANNAPOORNAM	57	F	PM	2271/12	MRM	R	U/I	2X2X1	N	_	FIRM	4	IDC	_	I
155	RANI	49	F	PrM	2273/12	MRM	R	U/O	4.5X4X3	N	_	gelatinous	5	MC	_	_
156	THANGAM	47	F	PrM	2293/12	MRM	L	U/O	5X4.5X3	N	_	FIRM	6	IDC	4	II
157	SHOBANA	49	F	PrM	2314/12	MRM	R	U/I	3x2.5x2	N	_	FIRM	9	IDC	1	II

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INTRODUCTION Breast cancer is a multifactorial disease which is having distinct biological subtypes. They have a broad spectrum of clinical, pathologic and molecular characteristic resulting in different prognosis and therapeutic applications. Therefore, every lump in the breast should be considered as a malignant lesion until proved otherwise. As breast is one of the frequent sites which is under the influence of hormones, major hormonal changes during adolescent period, child bearing period and at the time of menopause will affect the mammary tissue. Breast cancer is one among the frequently encountered malignancies in the world among females. There should be enough knowledge about its...